November 4, 2024

Comments from Scientists, Academics, and Clinicians on the Draft Risk Evaluation for Diisononyl Phthalate (DINP) Under TSCA

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These comments are submitted on behalf of the undersigned scientists, academics, and clinicians. We declare that we have no direct or indirect financial or fiduciary interests in the subjects of these comments. The co-signers' institutional affiliations are included for identification purposes only and do not imply institutional endorsement or support.

We appreciate the opportunity to provide written comments on EPA's Draft Risk Evaluation for Diisononyl Phthalate, (hereafter referred to as the *DINP Draft Risk Evaluation*) conducted under the Toxic Substances Control Act ("TSCA"), which requires EPA to evaluate chemical risks based on the "best available science."[1] DINP is a plasticizer used to make flexible polyvinyl chloride, and is also added to a variety of products including building and construction materials, automotive care and fuel products, and consumer products such as adhesives, sealants, paints, coatings, and electrical products.[2] Biomonitoring surveys indicate that most people living in the United States are exposed to DINP on a regular basis.[3] EPA has identified several health hazards of DINP exposure, including liver and developmental toxicity.[4]

In the DINP Draft Risk Evaluation, EPA has **failed to incorporate the best available science and makes a number of scientifically-unsupported assumptions that, if adopted, will result in acceptance of serious risks to human health and set a dangerous precedent for future TSCA risk evaluations**. For many conditions of use for DINP, there are serious inconsistencies between EPA's risk estimates and EPA's conclusions regarding unreasonable risk. EPA also repeatedly downplayed or disregarded the high risks it calculated without adequate scientific justification. For example, EPA used central tendency estimates of DINP exposure and risk for workers in most conditions of use in its unreasonable risk determination, thus disregarding unreasonable risks of non-cancer effects that may be faced by workers with exposures that are greater than median exposure levels. In doing so, EPA continues to set a dangerous precedent that risks to more highly-exposure individuals can be dismissed or downplayed without scientific support.

In addition, EPA has failed to adequately consider the scientific evidence and continued to rely on a systematic review methodology that is not consistent with best practices, violating TSCA's "best available science" requirement.[5] For example, EPA improperly excluded all human epidemiological studies from dose-response assessment and relied on systematic review methods that lacked transparency, and inappropriately excluded relevant health-effects studies from the

[1] 15 USC §2625(h).
[2] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), p. 10.
[3] Zota, A. R., Calafat, A. M., & Woodruff, T. J. (2014). Temporal Trends in Phthalate Exposures: Findings from the National Health and Nutrition Examination Survey, 2001–2010. Environmental Health Perspectives, 122(3), 235–241. https://doi.org/10.1289/ehp.1306681.
[4] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), p. 9.
[5] 15 U.S.C. § 2625(h).

hazard assessment without scientific justification. EPA's Science Advisory Committee on Chemicals ("SACC") recently criticized EPA's decision to disregard epidemiology studies in the dose-response assessment in the DINP Draft Risk Evaluation.[6] The National Academies of Sciences, Engineering, and Medicine ("NASEM") has recommended the use of existing systematic review methods and improved approaches for TSCA risk evaluations in 2021, and EPA has still not implemented most of these recommendations.[7] The SACC has also recommended best practices in systematic review to the Agency in multiple reports.[8] EPA should prepare a new TSCA systematic review methodology that is aligned with the best available scientific methods and issue updated draft systematic review protocols for all risk evaluations currently in development, including DINP.

The DINP Draft Risk Evaluation also relies on a dose-response assessment that violates TSCA's "best available science" requirement. While EPA found that developmental and liver toxicity are hazards of DINP, it failed to provide quantitative estimates of those non-cancer risks. We applied methods developed by the World Health Organization ("WHO") to quantify the risk of non-cancer liver toxicity from chronic DINP exposure, and found that EPA's current approach results in acceptance of exposures producing an upper bound risk of 1-in-200, a risk level *5,000 times higher* than the typical target risk level.

Another critical concern with the DINP Draft Risk Evaluation is EPA's failure to evaluate real world exposures and risks. For example, EPA fails to consider exposures from "non-TSCA" uses of DINP, including exposures through food and food packaging. Given that food is the primary route of exposure to both DINP in children and adults,[9] likely as a result of leaching from plastic food packaging materials, EPA will understate the risk to the general population from the TSCA uses of these chemicals if it does not take into account the background exposures from these and other non-TSCA uses. The SACC recently criticized EPA's decision to disregard exposures outside of the jurisdiction of TSCA.[10]

EPA also failed to adequately identify potentially exposed or susceptible subpopulations ("PESS") and calculate risks posed to these groups, as required under TSCA.[11] In the DINP Draft Risk Evaluation, EPA failed to consider individuals with pre-existing disease, genetic factors, lifestyle factors, geographic factors, or exposures to other chemical and non-chemical stressors that may increase susceptibility to harm from DINP exposure. A failure to evaluate risk to these groups violates TSCA and results in risk characterization that is not representative of the human population.

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[6] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," pp. 91-92.

[7] National Academies of Sciences, Engineering, and Medicine (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations.

[8] U.S. EPA (2022). Science Advisory Committee on Chemicals Meeting Minutes and Final Report No. 2022-2, p. 71. https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0414-0044.

[9] U.S. Consumer Product Safety Commission, *Report by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives* 102–03 (2014), pp. 3, 52–53, and 59.

[10] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," p. 16.

[11] 15 U.S.C. §§ 2602(12).

Finally, while we support and agree with EPA's decision to conduct a cumulative risk assessment for DINP and five other phthalates,[12] without the results of this assessment, EPA cannot make conclusions on unreasonable risk of DINP in a manner that adequately safeguards human health. EPA should therefore complete the planned phthalates cumulative risk assessment before finalizing the DINP unreasonable risk determination. Additionally, EPA should conduct a cumulative risk assessment for DINP and other chemicals sharing common adverse liver outcomes, consistent with the recommendations of the NASEM for cumulative risk assessment.[13]

Accordingly, EPA must make extensive revisions to the DINP Draft Risk Evaluation to more accurately characterize real-world exposures and risks, including to potentially exposed or susceptible subpopulations. This includes revising its risk determination for DINP to reflect quantitative non-cancer risk estimates, using high-end exposure and risk estimates, removing the use of any scientifically-unsupported justifications that downplay or disregard risk, and adopting best available scientific methods, like gold-standard systematic review methods that better account for and incorporate the scientific evidence.

Critical aspects of the present draft also warrant further SACC review before the DINP risk evaluation is finalized. Multiple aspects of the process of health effects evidence identification were not disclosed to the SACC prior to its review of the DINP draft hazard assessment; now that the DINP draft systematic review protocol has been released, the SACC should have the opportunity to review the procedures that are described in the protocol. The SACC recently cautioned that a much more extensive application of benchmark dose modeling is necessary to inform the selection of points of departure for DINP risk characterization,[14] and that epidemiology studies should not be excluded from the dose-response assessment.[15] Accordingly, EPA should conduct the necessary and recommended modeling and analysis for DINP, and the procedures and results should then be reviewed by the SACC.

Our detailed comments on the DINP Draft Risk Evaluation address the following issues:

1. **EPA's determination of unreasonable risk in occupational settings inappropriately discounts and disregards high-end exposures without justification and violates TSCA's requirement to assess risks to groups with greater exposures.**

2. **EPA's unreasonable risk determination disregards high risks to consumers from exposures to adhesives and sealants without justification.**

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[12] U.S. EPA (2023). Draft Proposed Principles of Cumulative Risk Assessment under the Toxic Substances Control Act.
[13] National Research Council (2008). Phthalates and Cumulative Risk Assessment: The Tasks Ahead.
[14] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," p. 92.
[15] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," pp. 91-92.

3. **EPA's non-cancer dose-response assessment for DINP is not consistent with the best available science.**
    a. **EPA improperly excluded human epidemiology studies from dose-response assessment.**
    b. **EPA failed to apply benchmark dose modeling to derive non-cancer points of departure for risk characterization.**
    c. **EPA's non-cancer margin of exposure (MOE) calculations are unreliable due to EPA's failure to conduct benchmark dose modeling.**
    d. **EPA should apply best available methods to generate quantitative estimates of non-cancer risks for varying levels of exposure to DINP.**

4. **EPA did not apply the best available science to identify and evaluate relevant and useful health effects studies for DINP.**
    a. **EPA did not conduct a comprehensive and up-to-date literature search.**
    b. **EPA relied on assessments conducted by other agencies to exclude studies, without supporting justification.**
    c. **EPA used deficient inclusion and exclusion criteria for health effects evidence that inappropriately excluded important toxicity endpoints.**
    d. **EPA used multiple strategies to inappropriately exclude PECO-relevant health effects studies.**
    e. **EPA continues to use unclear terminology regarding evidence synthesis and integration.**
    f. **EPA's approach to evidence integration lacks clear procedures and clearly-stated conclusions regarding the hazards of DINP.**
    g. **EPA released an incomplete draft systematic review protocol for DINP that was not made publicly available in advance of the draft risk evaluation.**
    h. **EPA should prepare a new TSCA systematic review handbook that is aligned with the best available scientific methods and issue updated draft systematic review protocols for all risk evaluations currently in development.**

5. **EPA failed to adequately identify potentially exposed or susceptible subpopulations (PESS), as required by TSCA.**

6. **EPA's approach systematically underestimates DINP exposure and risk.**
    a. **EPA failed to conduct a background exposure assessment, underestimating risk to potentially exposed or susceptible subpopulations.**
    b. **EPA considered aggregate exposure to only a limited extent.**

We appreciate the opportunity to provide public input. Please do not hesitate to contact us with any questions regarding these comments.

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1. **EPA's determination of unreasonable risk in occupational settings inappropriately discounts and disregards high-end exposures without justification and violates TSCA's requirement to assess risks to groups with greater exposures.**

In the DINP Draft Risk Evaluation, EPA determined that 2 occupational conditions of use (COUs) contribute to unreasonable risk, and the remaining 29 worker COUs do not contribute to unreasonable risk. For the 2 COUs contributing to unreasonable risk, EPA used high-end exposure and risk estimates in making this determination. For the majority of COUs not contributing to unreasonable risk, EPA improperly based its determination on "central tendency" estimates of exposure and risk. EPA's explanation of these key terms is as follows:

> The central tendency is expected to represent occupational exposures in the center of the distribution for a given COU…EPA preferred to provide the 50th percentile of the distribution. However, if the full distribution was unknown, EPA used either the mean, mode, or midpoint of the distribution to represent the central tendency depending on the statistics available for the distribution. The high-end exposure is expected to represent occupational exposures that occur at probabilities above the 90th percentile, but below the highest exposure for any individual (U.S. EPA, 1224 1992). For risk evaluation, EPA provided high-end results at the 95th percentile. If the 95th percentile was not reasonably available, EPA used a different percentile greater than or equal to the 90th percentile but less than or equal to the 99th percentile, depending on the statistics available for the distribution. If the full distribution is not known and the preferred statistics are not reasonably available, EPA estimated a maximum or bounding estimate in lieu of the high-end.[16]

EPA's exposure assessment (Tables 4-3 and 4-4) and risk characterization (Table 4-17) provide both central tendency and high-end estimates for each COU, but for most COUs, EPA used only central tendency values in determining unreasonable risk, without acknowledging that it has therefore disregarded the potential unreasonable risks to workers with exposures greater than the central tendency.

EPA repeatedly states that it is using the central tendency for the unreasonable risk determination because these values are the most representative of worker exposures for the COU. For example:

> In summary, it was determined that the central tendency estimates of worker exposure and risk are most representative for all manufacturing, processing, industrial and commercial COUs—with exception of some industrial COUs for Adhesive and sealant chemicals and Paints and coatings due to the potentially elevated inhalation exposures from pressurized spray operations.[17]

> Exposures from low-pressure spray applications (*e.g.,* HVLP spray guns) are best represented by central tendency estimates.[18]

[16] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), p. 66.
[17] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), p. 140.
[18] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), p. 141.

> Due to the uncertainty of DINP concentrations in workplace dust, central tendency values of exposure are expected to be most reflective of worker exposures within the COUs covered under the PVC plastics compounding and Non-PVC material compounding OESs.[19]
>
> If the frequency of use and/or the amount of DINP is overestimated, this leads to a level of uncertainty in the high-end estimates, and therefore, the central tendency estimates would be more representative of the exposure for some COUs.[20]

EPA's statements are not a justification for using central tendency estimates, but rather are reiteration of the definition of central tendency. These statements disregard the Agency's obligation under TSCA to determine whether workers with greater-than-typical exposures are experiencing an unreasonable risk.[21] Further, uncertainty is not a defensible basis for disregarding potential risks to more-exposed workers.

EPA's Science Advisory Committee on Chemicals (SACC) recently commented on the unexpected and unjustified change from EPA's practice in previous TSCA risk evaluations:

> For occupational exposures, central tendency and 95 centile exposures were evaluated, but only the central tendency conditions were carried through to the risk characterization. EPA should justify why the pivot from past practice, when it is noted that the benchmark was exceeded for some COUs using the 95th centile exposure conditions.[22]

The practice of utilizing high-end exposure estimates is scientifically well-supported and is consistent with both the requirements of TSCA[23] and previous TSCA risk evaluations. This approach is crucial for ensuring that the risk evaluation comprehensively addresses all potential risks, particularly to the most vulnerable and highly exposed groups within the workforce.

EPA's application of the central tendency estimates instead of high-end exposure estimates in the DINP Draft Risk Evaluation effectively disregards potential unreasonable risks to workers for the majority of COUs evaluated. This raises significant concerns about the adequacy and methods of the risk evaluation. The justification provided by the EPA for excluding high-end exposure estimates lacks supporting evidence. For example, EPA asserts that high-end inhalation exposure estimates typically represent high-pressure spray applications and suggests that central tendency estimates are more reflective of low-pressure applications, including non-spray methods.[24] However, EPA presents no evidence to support the notion that high-end exposures are an overestimation or that such exposure scenarios are unlikely to occur. Moreover, EPA's sole reliance on central tendency estimates likely underestimates exposures in scenarios that do not conform to this median.

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[19] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), p. 144.
[20] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), p. 189.
[21] 15 U.S.C. § 2605(b)(4)(A).
[22] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," p. 19.
[23] 15 U.S.C. § 2605(b)(4)(A).
[24] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), pp. 140-141.

More critically, the use of central tendency estimates fails to consider the risk to individuals exposed at levels above this median, disregarding the potential for health risks to as much as half of the exposed population. This approach does not align with TSCA's mandate to identify and protect potentially exposed or susceptible subgroups (PESS), characterized by greater exposure levels than the general population.[25]

Applying only central tendency estimates for the risk evaluation also means that EPA will potentially overlook significant risks, particularly for workers engaged in high-exposure tasks or those exposed to multiple chemical and non-chemical stressors. Special consideration should be given to more vulnerable workers, including women of reproductive age and other PESS, who might face heightened risks even at lower levels of exposure.

To adhere to the requirements of TSCA and to ensure robust protection for all workers, the EPA should employ high-end exposure estimates that represent at least the 95th percentile of exposure—preferably even higher, such as the 99th percentile. This adjustment is necessary to accurately reflect the risk for the most exposed individuals and to ensure that all COUs are evaluated with an appropriate level of concern, particularly those currently deemed as less certain or not contributing to unreasonable risk.[26]

Given the EPA's existing high-end worker exposure estimates presented in the DINP Draft Risk Evaluation, the Agency's unreasonable risk determination has disregarded significant worker risks for multiple COUs. According to the text and Table 4-17, high-end risk estimates are at levels indicating unreasonable risk for the following occupational exposure scenarios:

- PVC Plastics Compounding
- Non-PVC Material Compounding
- PVC Plastics Converting
- Non-PVC Material Converting
- Recycling
- Disposal.

It is also concerning that EPA chose to disregard high-end risk estimates at the final stages of the risk evaluation, only after finding (in Table 4-17) high risks for the compounding, converting, recycling and disposal scenarios. For example, the discussion of PVC Plastics Compounding in EPA's Draft Environmental Release and Occupational Exposure Assessment for DINP makes no mention of any excessive uncertainties that undermine confidence in the high-end exposure estimate, and its weight of the scientific evidence conclusion finds that the estimates are plausible:

[25] 15 U.S.C. § 2605(b)(4)(A).
[26] 15 U.S.C. §2602(12).

> Based on this information, EPA concluded that the weight of scientific evidence for this assessment is moderate, and the assessment provides a plausible estimate of releases, considering the strengths and limitations of the reasonably available data.[27]

In fact, EPA concluded that the weight of the scientific evidence for **all** occupational exposures scenarios was "moderate" and the estimates were "plausible."[28] If EPA's exposure assessors had any concerns about the representativeness of either the central tendency or high-end exposure estimates, those would have been stated in the Draft Environmental Release and Occupational Exposure Assessment. Further, no significant concerns regarding the estimates are stated in the Occupational Exposures section of the DINP Draft Risk Evaluation (Section 4.1.1). Instead, this section describes the strengths of the assessment as:

> The exposure scenarios and exposure factors underlying the inhalation and dermal assessment are supported by moderate to robust evidence. Occupational inhalation exposure scenarios were informed by moderate or robust sources of surrogate monitoring data or GSs/ESDs used to model the inhalation exposure concentration. Exposure factors for occupational inhalation exposure include duration of exposure, body weight, and breathing rate, which were informed by moderate to robust data sources.
>
> A strength of the modeling assessment includes the consideration of variable model input parameters as opposed to using a single static value. Parameter variation increases the likelihood that the true occupational inhalation exposures fall within the range of modeled estimates. An additional strength is that all data that EPA used to inform the modeling parameter distributions have overall data quality ratings of either high or medium from EPA's systematic review process. Strengths associated with dermal exposure assessment are described in Table 4-5.[29]

The concluding text regarding limitations, assumptions and uncertainties in the Occupational Exposures section of the DINP Draft Risk Evaluation notes uncertainties in the available data but does not mention any concerns regarding the representativeness of the high-end exposure estimates.

Instead, the questions regarding representativeness of some estimates are raised only in the Risk Characterization and Unreasonable Risk Determination sections of the Draft DINP Risk Evaluation – sections that can be drafted only after risks have been calculated using the central tendency and high-end exposure estimates. The placement of the statements raising doubts about the high-end exposure estimates seems to indicate that EPA developed these concerns only after finding that the high-end exposures led to risk estimates that represent unreasonable risks.

EPA does not provide sufficient evidence in the DINP Draft Risk Evaluation for its claims that the high-end estimates are not representative of exposures for at least some workers. EPA further

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[27] U.S. EPA (2024). Draft Environmental Release and Occupational Exposure Assessment for Diisononyl Phthalate (DINP), p. 146.
[28] U.S. EPA (2024). Draft Environmental Release and Occupational Exposure Assessment for Diisononyl Phthalate (DINP), Table 4-1.
[29] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), p. 85.

does not present evidence justifying the use of central tendency estimates to characterize exposures and risks to all workers in each COU. If EPA did have evidence that its current "high-end" estimates are not representative of high-end exposures for a given COU, the appropriate action would be to then develop new high-end estimates rather than relying only on the central tendency estimates.

Ignoring calculated risk at the final stage of the draft risk evaluation based on flawed and scientifically unsupported rationales undermines the integrity of the risk estimates, and suggests that EPA is disregarding high-end estimates solely to avoid determining a contribution to unreasonable risk for each occupational COU. EPA must adopt a more transparent, consistent, and accountable approach to risk assessment. Uncertainties identified by EPA must be addressed early in the exposure assessment; all reasonably foreseeable exposures, including high-end exposures for each occupational exposure scenario and COU must be accounted for; and the unreasonable risk determination must not disregard high-end exposure estimates developed in the exposure assessment component of conducting a risk evaluation.

In addition, EPA's attempts to justify disregarding the high-end estimates, including repeated mentions of uncertainties and lack of data, indicate that EPA failed in its obligation to ensure that it obtained the necessary data needed to conduct a defensible risk evaluation. This is particularly concerning for a manufacturer-requested risk evaluation, where, according to the preamble to the original risk evaluation framework rule (which was in place at the time EPA granted the request), the

> manufacturers are required to submit all the information necessary to complete risk evaluation[30]

Further, according to the framework rule, EPA should have initiated the risk evaluation only if it had obtained the necessary data from the manufacturers:

> EPA will grant the request if it determines that…EPA has the required information necessary for conducting a risk evaluation…Bases for a denial, include the manufacturer has not provided sufficient information to complete the risk evaluation.[31]

Even having granted the manufacturer request without adequate data, there are no indications that EPA utilized its authority under TSCA to obtain data after initiating the DINP Draft Risk Evaluation. Given the potentially significant data gaps, EPA's high-end exposure estimates make appropriate use of the reasonably available data and should be used as the basis for the unreasonable risk determination.

[30] 82 FR 33726.
[31] 40 CFR § 702.37(e)(6).

2. EPA's unreasonable risk determination disregards high risks to consumers from exposures to adhesives and sealants without justification.

EPA's DINP Draft Risk Evaluation determines that one consumer COU, floor coverings, contributes to unreasonable risk. EPA estimated high risks for a second COU, adhesives and sealants, but determined that these products do not contribute to unreasonable risk despite the high risk estimates. Table 6-2 does indicate an unreasonable risk finding for the adhesives and sealants COU based on chronic non-cancer health effects, but the text states that the only consumer COU contributing to unreasonable risk is floor coverings. The inconsistency between the table and the text suggests that EPA may have initially identified consumer adhesives and sealants as a contributor to unreasonable risk, but then later attempted to justify disregarding the risks posed by DINP for this COU in the risk determination section.

EPA explains that the high risk estimates for consumer adhesives and sealants are based on a scenario of do-it-yourself work with roofing adhesives. It then states that there are significant uncertainties in the exposure estimate that could not be quantified, and concludes that exposure is overestimated. EPA does not present substantial evidence to conclude that exposures are overestimated, and does not present alternative exposure estimates, but instead simply decides to disregard the exposures and risks that it has estimated, stating that it is:

> unable to quantify the uncertainty from aggregating conservative risk estimates of inhalation and dermal routes of exposure, resulting in an aggregate MOE that overestimates the risk. Therefore, EPA is preliminarily determining that the consumer COU Construction, paint, electrical, and metal products – adhesives and sealants, in an outdoors or well-ventilated setting, does not contribute significantly to the unreasonable risk of DINP.[32]

It is particularly concerning that EPA chose to disregard the risk estimates for this COU at the final stages of the risk evaluation – that is, the unreasonable risk determination in section 6 of the DINP Draft Risk Evaluation—only after finding (in Table 4-18) high chronic non-cancer risks to young teens, teenagers, and adults. This decision is not supported by EPA's more detailed discussion of the consumer exposure estimates. Specifically, the draft DINP consumer exposure document concludes that the weight of scientific evidence for the adhesives and sealants COU is "robust" for inhalation and "moderate"[33] for dermal exposure, with the only uncertainty noted being the rate of absorption through the skin. The same statements are provided in the Consumer Exposures section of the DINP Draft Risk Evaluation (section 4.1.2).[34] Thus, the more in-depth presentations of the consumer exposure assessment raised no issues that could call into question the use of the estimated exposure for the adhesives and sealants COU in determining unreasonable risk. If EPA's exposure assessors had any significant concerns about the exposure estimates that would preclude their use in determining unreasonable risk, those would have been stated in the Draft Consumer and Indoor Exposure Assessment.

[32] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), p. 200.
[33] U.S. EPA (2024). Draft Consumer and Indoor Exposure Assessment for Diisononyl Phthalate (DINP), Table 5-1.
[34] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), Table 4-9.

Instead, the questions regarding the estimates are raised only in the Unreasonable Risk Determination section of the Draft DINP Risk Evaluation—text that can be drafted only after risks have been calculated using the exposure estimates developed in the Draft Consumer and Indoor Exposure Assessment and presented in the Consumer Exposures section of the DINP Draft Risk Evaluation. The placement of the statements describing the estimates as too uncertain for use in determining unreasonable risk seems to indicate that EPA developed these concerns only after finding that the exposure levels led to risk estimates that represent unreasonable risks.

If EPA had legitimate concerns regarding the consumer exposure estimates for adhesives and sealants, the appropriate action would be to develop new estimates rather than simply disregarding the potential risk to consumer do-it-yourselfers altogether. Ignoring calculated risk at the final stage of the draft risk evaluation based on flawed and scientifically unsupported rationales undermines the integrity of the risk estimates, and suggests that EPA is disregarding its own estimates solely to avoid determining a contribution to unreasonable risk. EPA must adopt a more transparent, consistent, and accountable approach to TSCA unreasonable risk determination. Uncertainties identified by EPA must be addressed early in the exposure assessment; all reasonably foreseeable exposures, including high-end exposures for each consumer exposure scenario and COU must be accounted for; and the unreasonable risk determination must not disregard high-end exposure estimates developed in the exposure assessment component of conducting a risk evaluation.

In addition, EPA's attempts to justify disregarding certain exposure and risk estimates, including repeated mentions of uncertainties and lack of data, indicate that EPA failed in its obligation to ensure that it obtained the necessary data needed to conduct a defensible risk evaluation. As noted above, this is particularly concerning for a manufacturer-requested risk evaluation, where, according to the preamble to the original risk evaluation framework rule (which was in place at the time EPA granted the request), the

> manufacturers are required to submit all the information necessary to complete risk evaluation[35]

Further, according to the framework rule, EPA should have initiated the risk evaluation only if it had obtained the necessary data from the manufacturers:

> EPA will grant the request if it determines that…EPA has the required information necessary for conducting a risk evaluation…Bases for a denial, include the manufacturer has not provided sufficient information to complete the risk evaluation.[36]

EPA's decision that it lacks sufficient data to make an unreasonable risk determination for consumer adhesives and sealants contradicts EPA's earlier determination, in granting the manufacturer request, that it had all of the necessary information needed to conduct a risk evaluation for DINP. EPA's consumer exposure estimates for adhesives and sealants make appropriate use of the reasonable available data. The appropriate course of action is to conclude that the consumer adhesives and sealants COU contributes to the unreasonable risk of DINP.

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[35] 82 FR 33726.
[36] 40 CFR § 702.37(e)(6).

An additional concern regarding risks to consumers is that the DINP Draft Risk Evaluation is not clear on whether EPA has determined that wallpaper contributes to the unreasonable risk of DINP. Table 4-18 of the DINP Draft Risk Evaluation clearly identifies wallpaper as a use of DINP with high chronic non-cancer risk to all childhood age groups up through age 10. However, it is unclear if this use is included in the floor coverings COU (identified by EPA as a contributor to unreasonable risk), as the full name of the COU for floor coverings makes no mention of wall coverings or any use of the word "wall:"

> Consumer use – furnishing, cleaning, treatment/care products – floor coverings/plasticizer in construction and building materials covering large surface areas including stone, plaster, cement, articles; fabrics, textiles and apparel (vinyl tiles, resilient flooring, PVC-backed carpeting).[37]

Regardless of the particular COU, EPA must clearly identify wallpaper as a contributor to unreasonable risk in the final DINP risk evaluation.

3. EPA's non-cancer dose-response assessment for DINP is not consistent with the best available science.

a. EPA improperly excluded human epidemiology studies from dose-response assessment.

In the DINP Draft Hazard Assessment, EPA identified (primarily through public submissions to the docket) more than 50 recent human epidemiology studies of DINP non-cancer effects, using biomonitoring of urinary metabolites as measures of exposure. EPA excluded all of these studies from its dose-response analysis, without any consideration of the strengths and weaknesses of each individual study:

> The Agency did not use epidemiology studies quantitatively for dose-response assessment, **primarily due to uncertainty associated with exposure characterization.** Primary sources of uncertainty include the source(s) of exposure; timing of exposure assessment that may not be reflective of exposure during outcome measurements; and use of spot-urine samples, which due to rapid elimination kinetics may not be representative of average urinary concentrations that are collected over a longer term or calculated using pooled samples. Additional uncertainty results from co-exposure to mixtures of multiple phthalates that may confound results for the majority of epidemiologic studies, which examine one phthalate and one exposure period at a time such that they are treated as if they occur in isolation.[38] (emphasis added)

EPA's blanket exclusion of an entire category of studies is scientifically inappropriate and violates the TSCA requirement to use the best available science.[39] The preamble to EPA's recent

[37] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), pp. 12-13.
[38] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), pp. 12-13.
[39] 15 USC §2625(h).

final framework rule for conducting risk evaluations re-stated EPA's commitment to systematic review:

> EPA believes that integrating appropriate and applicable systematic review methods into the TSCA risk evaluations is critical to meeting the scientific standards as described in TSCA section 26(h) and (i)…. The principles of systematic review are well-established and include "transparent and explicitly documented methods, consistent and critical evaluation of all relevant literature, application of a standardized approach for grading the strength of evidence, and clear and consistent summative language" (Ref. 26). EPA has finalized the requirement to use and document systematic review methods to assess reasonably available information.[40]

EPA's broad exclusion of DINP epidemiology studies from dose-response analysis is contrary to the framework rule preamble and disregards the structured, consistent systematic review process that is required to evaluate the quality of relevant epidemiological studies according to pre-specified criteria. EPA has effectively ignored its systematic review process and excluded studies from dose-response assessment with an argument that demonstrates a bias against environmental epidemiology, rather than a thoughtful approach to evidence evaluation that is consistent with best practices in systematic review.

EPA's SACC criticized EPA's decision to disregard the epidemiology studies:

> Several recent human epidemiology studies of DINP non-cancer effects, including developmental effects were excluded from the dose-response assessment. These studies were excluded because of uncertainty about exposure. However, the studies focused on measurement of urinary biomarkers of phthalates, including metabolites of DINP. While there are technical issues when using urinary biomarkers for determination of exposure, this is a common approach and the gold standard for phthalates to understand the association between the chemicals and outcomes relevant in people. EPA individually assessed the merits of 53 epidemiology studies of DINP, published from 2018 to 2021, applying a pre-specified set of study quality domains and metrics that closely mirrors the approach used by EPA's IRIS program, which has been favorably reviewed by the NASEM. EPA's overall quality determination was "Medium" or "High" for 46 of these epidemiology studies. Each study was individually assessed for its exposure measurement methods (Domain 2) and treatment of potential confounding (Domain 4).[41]

The SACC then provided this recommendation to EPA:

> EPA has disqualified epidemiology studies in a manner inconsistent with its own pre-specified procedures. EPA's own overall quality determinations indicate that these studies

[40] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act (TSCA). 89 FR 37028.

[41] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," p. 91.

are suitable for use. EPA should include these studies in its identification of studies potentially suitable for informing a POD.[42]

As pointed out by the SACC, the issues that EPA raises in an attempt to disqualify the entire set of epidemiology studies have already been accounted for in a systematic manner using pre-specified procedures to assess the quality of each study, including domains for exposure assessment and potential confounding. EPA's own study quality assessments indicate that these studies are consistent with existing standards for use of studies in dose-response assessment.

Moreover, EPA's explanation considers only alleged limitations of the DINP epidemiologic studies as a class, without considering strengths of these studies (e.g., they are conducted in humans rather than laboratory animals, at exposure levels routinely experienced by humans) or mitigating considerations (e.g. regression models that control for co-exposures; implications of exposure misclassification) that apply to the limitations. For example, the use of spot-urine samples is a limitation that is expected to result in some degree of exposure misclassification, but to the extent this occurs, it is likely to result in underestimation of risks. In general, the uncertainties in exposure characterization may result in exposure misclassification that biases dose-response estimates towards the null, but that does not mean the studies are not useful or informative and potentially strong candidates for determination of the point of departure (POD).

In an attempt to support its decision to disregard epidemiological studies, EPA cites similar decisions made in previous DINP assessments conducted by other agencies. However, the most recent of these previous assessments considered literature published only up to January 2018, whereas the 53 epidemiology studies assessed for study quality by EPA were all published from 2018-2021, and were therefore not considered in the previous assessments referenced by EPA.

EPA does not provide any scientific justification for disregarding its own conclusions regarding these studies when evaluated individually, and by overriding the findings of the systematic review process, EPA has therefore violated TSCA's requirement to use the best available science.[43] EPA cannot broadly exclude epidemiologic studies from dose-response assessment in the DINP Draft Risk Evaluation, and must consider each relevant study on an individual basis as a candidate for POD derivation.

b. EPA failed to apply benchmark dose modeling to derive chronic non-cancer points of departure for risk characterization.

EPA violated its own commitment to use EPA guidance in conducting TSCA risk evaluations by not applying benchmark dose (BMD) modeling to derive chronic non-cancer points of departure for risk characterization of DINP. EPA has therefore not used the best available science and leaves uncertainty regarding whether the most sensitive studies and endpoints were selected for use in estimating risks.

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[42] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," p. 92.
[43] 15 USC §2625(h).

The SACC commented that much more thorough BMD modeling of multiple studies should be conducted to inform selection of the point of departure for DINP:

> EPA should use all available dose range studies from which BMD-based POD should be developed, compared with each other to select the lowest BMD-based POD as the basis for the derivation for the HED.[44]
>
> EPA should apply benchmark dose modeling to derive chronic non-cancer points of departure and select the one that is most sensitive (lowest).[45]

For risk characterization of chronic exposure to DINP, EPA proposed to use the chronic no-observed-adverse-effect level (NOAEL) for liver toxicity of 15 mg/kg-day (applied dose) from a 2-year dietary study in rats by Lington *et al.* After application of default allometric scaling, the POD is a human equivalent dose (HED) of 3.5 mg/kg-day. EPA says it has "robust overall confidence"[46] in this POD, but EPA's flawed dose-response assessment procedures for DINP do not support that conclusion.

In Table 4-5 of the DINP Draft Hazard Assessment, EPA displays 12 NOAEL and lowest-observed adverse-effect level (LOAEL) values for liver, kidney and developmental toxicity that were candidates for the chronic POD. The NOAEL HED values range from 3.5 to 48.5 mg/kg-day, and the LOAEL HEDs are from 14 to 89 mg/kg-day.[47] EPA chose the Lington *et al.* developmental toxicity NOAEL as the POD because it was more sensitive (i.e., lower) than all other candidate NOAELs and LOAELs.

Using a NOAEL as the POD rather than a benchmark dose (BMD) is not consistent with the best available science, as stated in EPA guidance[48] and reports from the NASEM.[49,50] By disregarding its own 2012 *Benchmark Dose Technical Guidance* in conducting dose-response analysis for DINP, EPA has violated its recent final rule *Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act (TSCA)*, which states:

> EPA will use applicable EPA guidance when conducting risk evaluations, as appropriate and where it represents the best available science.[51]

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[44] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," p. 92.
[45] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," p. 92.
[46] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), p. 89.
[47] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), Table 4-5.
[48] U.S. EPA (2012). Benchmark Dose Technical Guidance.
[49] NASEM (2017). Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active chemicals, p. 158.
[50] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 129.
[51] 40 CFR § 702.37.

The Benchmark Dose Technical Guidance document is appropriate and represents the best available science, and it clearly states that NOAELs and LOAELs are significantly limited:

> The NOAEL is actually of little practical utility in describing toxicological dose-response relationships; it does not represent a biological threshold and cannot establish that lower exposure levels are necessarily without risk. Specific limitations of the NOAEL/LOAEL approach are well known and have been discussed extensively (Crump 1984; Gaylor 1983; Kimmel and Gaylor 1988; Leisenring and Ryan 1992; U.S. EPA 1995a):
>
> - The NOAEL/LOAEL is highly dependent on sample size. The ability of a bioassay to distinguish a treatment response from a control response decreases as sample size decreases, so the NOAEL for a compound (and thus the POD, when based on a NOAEL) will tend to be higher in studies with smaller numbers of animals per dose group.
> - More generally, the NOAEL/LOAEL approach does not account for the variability and uncertainty in the experimental results that are due to characteristics of the study design such as dose selection, dose spacing, and sample size.
> - NOAELs/LOAELs do not correspond to consistent response levels for comparisons across studies/chemicals/endpoints, and the observed response level at the NOAEL or LOAEL is not considered in the derivation of RfDs/RfCs.
> - Other dose-response information from the experiment, such as the shape of the dose-response curve (e.g., how steep or shallow the slope is at the BMD, providing some indication of how near the POD might be to an inferred threshold), is not taken into account…
> - While the NOAEL has typically been interpreted as a threshold (no-effect level), simulation studies (e.g., Leisenring and Ryan 1992; study designs involving 10, 20, or 50 replicates per dose group) and re-analyses of developmental toxicity bioassay data (Gaylor 1992; Allen et al. 1994a; studies involving approximately 20 litters per dose group) have demonstrated that the rate of response above control at doses fitting the criteria for NOAELs, for a range of study designs, is about 5–20% on average, not 0%.[52]

The Benchmark Dose Technical Guidance further states that use of a BMD/BMDL as a POD is preferred and a NOAEL or LOAEL should be considered as a POD only if BMD modeling is conducted and is unable to produce a BMD estimate, and requires justification:

> Because of the limitations of the NOAEL/LOAEL approach discussed earlier, the BMD approach is preferred to the NOAEL/LOAEL approach… there are some instances in which reliable BMDs cannot be estimated and the NOAEL/LOAEL approach might be warranted…In such cases, the NOAEL/LOAEL approach might be used, while recognizing its limitations and the limitations of the dataset.[53]

[52] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 4.
[53] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 6.

> Resorting to the NOAEL/LOAEL approach does not resolve a data set's inherent limitations, but it conveys that there are limitations with the data set.[54]
>
> At times, modeling will not yield useful results and the NOAEL/LOAEL approach might be considered, although the data gaps and inherent limitations of that approach should be acknowledged.[55]
>
> In some cases, modeling attempts may not yield useful results. When this occurs and the most biologically relevant effect is from a study considered adequate but not amenable to modeling, the NOAEL (or LOAEL) could be used as the POD. The modeling issues that arose should be discussed in the assessment, along with the impacts of any related data limitations on the results from the alternate NOAEL/LOAEL approach.[56]

EPA cited the Benchmark Dose Technical Guidance in a previous TSCA risk evaluation to describe the preference for a BMD over a NOAEL:

> As outlined in EPA guidance, the BMD approach overcomes many of the limitations inherently associated with the NOAEL/LOAEL approach, and thus is the preferred method for establishing a POD for use in risk assessment.[57]

EPA's 2022 handbook for conducting chemical hazard assessments for the Integrated Risk Information System (IRIS) reinforces these key points:

> As discussed in detail in Section 1.2 of EPA's Benchmark Dose Technical Guidance (U.S. EPA, 2012b), dose-response modeling (i.e., benchmark dose modeling) is the preferred approach for deriving points of departures given several limitations in the no-observed adverse-effect level/ lowest-observed-adverse-effect level (NOAEL/LOAEL) approach.[58]
>
> Basis of the POD: A modeled BMDL is preferred over a NOAEL, which is in turn preferred over a LOAEL.[59]

Reports from the NASEM also state the advantages of BMD modeling. The NASEM report on low-dose toxicity of endocrine active chemicals (which was the source of the BMDL selected as POD for acute effects of DINP) discusses the deficiencies of the NOAEL/LOAEL approach for risk estimation:

> The use of LOAELs and NOAELs is less than ideal because they depend highly on individual study-design characteristics; therefore, apparent differences among studies

[54] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 12.
[55] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 30.
[56] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 40.
[57] U.S.EPA (2020). Risk Evaluation for n-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) (NMP), p. 262.
[58] U.S. EPA (2022). ORD Staff Handbook for Developing IRIS Assessments, p. 8-1.
[59] U.S. EPA (2022). ORD Staff Handbook for Developing IRIS Assessments, p. 8-18.

> might be explained by design differences, such as sample size or dose spacing, rather than true inconsistency.[60]

In the 2009 report *Science and Decisions*, the National Academies highlighted the adoption of the BMD approach as an important improvement in risk assessment methodology:

> Another refinement in dose-response assessment has been the derivation of the RfD or low-dose cancer risk from a POD that is calculated using BMD methodology (EPA 2000a). In noncancer risk assessment, this approach has the advantage of making better use of the dose-response evidence available from bioassays than do calculations based on NOAELs. It also provides additional quantitative insight into the risk presented in the bioassay at the POD because for quantal end points the POD is defined in terms of a given risk for the animals in the study.[61]

EPA did conduct BMD modeling of multiple endpoints from the Lington *et al*. study, but then chose to use the NOAEL rather than a lower bound BMD value (BMDL) as the POD, which directly conflicts with the EPA Benchmark Dose Technical Guidance, EPA IRIS handbook, previous TSCA risk evaluations, and NASEM recommendations. The EPA-estimated BMDLs for some endpoints were lower than the NOAEL. EPA chose not to use the BMDL of 8.6 mg/kg-day (applied dose) for spongiosis hepatis in the liver or the BMDL of 15.5 mg/kg-day for serum ALT at 6-month sacrifice[62] as the chronic POD, instead using the NOAEL as the chronic POD without appropriate scientific justification:

> The wide variability in BMDLs and uncertainty in several modelled outcomes (*i.e.,* BMD/BMDL ratios greater than 3) reduce EPA's confidence in using the BMD modeling results for establishing a POD, and further affirm the use of the NOAEL for establishing the POD.[63]

Variability in BMDLs across endpoints is not a valid justification for using a NOAEL rather than a BMDL; EPA guidance (see above) instead emphasizes the strong preference for using a BMDL rather than a NOAEL. EPA's mention of BMD/BMDL ratios is also not supported by EPA guidance, and furthermore is not valid because the BMD/BMDL ratio for increased serum ALT is only 1.5 (23.4 / 15.5 = 1.5).[64]

EPA's attempt to justify using a NOAEL as POD continues:

> EPA considers it more appropriate to use the NOAEL of 15 mg/kg-day instead of the BMD05 of 12 mg/kg-day because the NOAEL supports the suite of effects on the liver

[60] NASEM (2017). Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active chemicals, p. 158.
[61] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 129.
[62] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), Table_Apx E-1.
[63] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), p. 89.
[64] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), Table_Apx E-7.

> occurring at 152 mg/kg-day instead of being based on the single effect of spongiosis hepatis with its associated uncertainty regarding human relevance.[65]

This explanation also is not scientifically valid. First, EPA uses an inappropriate comparison of the NOAEL to a BMD value, when the lower-bound estimate of the BMD (i.e. the $BMDL_{05}$) is the appropriate choice. Second, the mention of the term "suite of effects" disregards the fact that the BMD analysis shows that, as one would expect, some liver effects are more sensitive than others; the use of the term "suite of effects" averages over multiple outcomes to obscure the most sensitive outcomes, contrary to the objective of selecting the most sensitive endpoint. Finally, EPA does not give any rationale for disregarding the increased serum ALT BMDL of 15 mg/kg-day in selecting the POD.

Further, EPA did not conduct BMD modeling for any of the candidate chronic PODs other than the liver effects from Lington *et al.* This means that EPA has not applied the best available science to determine the most sensitive endpoint, as it selected the POD without conducting appropriate dose-response analysis and instead relied on comparisons of NOAELs and LOAELs. EPA's Benchmark Dose Technical Guidance clearly states that identification of the most sensitive endpoint cannot be based on comparisons of NOAELs, and that all candidate values should be evaluated based on BMD modeling:

> The apparent relative sensitivities of endpoints based on NOAELs/LOAELs may not correspond to the same relative sensitivities based on BMDs or BMDLs after BMD modeling; therefore, relative sensitivities of endpoints cannot necessarily be judged a priori. For example, differences in slope (at the BMR) among endpoints could affect the relative values of the BMDLs. Selected endpoints from different studies that have the potential to be used in the determination of a POD(s) should all be modeled.[66]

A BMDL is frequently lower than the NOAEL for the same endpoint, and frequently much lower than the LOAEL for the same endpoint. Without BMD modeling, EPA is unable to make a scientific determination of whether the findings from Lington *et al*. study are more sensitive than the liver effects from Bio/dynamics 1987 (NOAEL HED = 6.4 mg/kg-day), kidney lesions from Hazleton labs (*LOAEL* HED = 14.2 mg/kg-day), developmental effects from Waterman *et al*. (*LOAEL* HED = 31.4 mg/kg-day), or other candidate endpoints.[67] The scientifically appropriate method for selecting the POD based on the most sensitive endpoint would be to estimate a BMDL for each endpoint, and then select the lowest value.

By disregarding existing EPA guidance and NASEM recommendations that state BMD modeling is the most scientifically appropriate approach for determining the POD, EPA violates the TSCA section 26(h) scientific standards which direct that the Agency:

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[65] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), p. 89.
[66] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 15.
[67] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), Table 4-5.

> Shall use scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science.[68]

Further, EPA's recently promulgated revisions to the framework rule for TSCA risk evaluations states that:

> EPA will document that the risk evaluation is consistent with the best available science.[69]

EPA cannot ensure that the final DINP risk evaluation meets this requirement unless it has implemented BMD modeling in the process of selecting a POD.

c. EPA's non-cancer margin of exposure (MOE) calculations are unreliable due to EPA's failure to conduct benchmark dose modeling.

To inform its determination of unreasonable risks of non-cancer effects from chronic exposure, EPA calculated a margin of exposure (MOE) for each DINP condition of use (COU) using the human equivalent dose (HED) of the Lington *et al.* liver toxicity NOAEL POD, which is 3.5 mg/kg-day.[70] The MOE is calculated as:

> Margin of Exposure = Non-cancer point of departure / Human exposure.

As discussed below, the MOE approach is a scientifically deficient method for characterizing risk and is inconsistent with amended TSCA's requirements to use the "best available science"[71] and to ensure protection of "potentially exposed and susceptible subpopulations" ("PESS").[72]

In the DINP Draft Risk Evaluation, the many shortcomings of EPA's MOE approach are exacerbated by EPA's failure to conduct dose-response modeling. EPA's calculated MOEs for DINP are in question because of EPA's use of a NOAEL as the POD, and because it failed to conduct BMD modeling for studies other than Lington *et al*., which may have yielded a lower POD. Application of BMD modeling could result in a POD that is significantly lower than the Lington *et al.* NOAEL, which in turn would significantly reduce the calculated MOEs. COUs that currently have calculated MOEs up to 100 or even greater could conceivably be reduced to below EPA's benchmark MOE of 30 when recalculated with an appropriate POD, and should be provisionally considered contributors to unreasonable risk until EPA has conducted BMD modeling of multiple non-cancer endpoints and, preferably, conducted a probabilistic dose-response analysis, as described below, to replace the MOE approach. The COUs for which a conclusion that the chronic MOE is greater than 30 is questionable due to EPA's deficient approach to dose-response analysis include:[73]

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[68] 15 U.S.C. § 2625(h).
[69] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act (TSCA). 89 FR 37028, May 3, 2024, § 702.37(a)(2).
[70] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), Table 4-16.
[71] 15 U.S.C. §2625 (h).
[72] 15 U.S.C. §2602 (12).
[73] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), Table 4-17 and Table 4-18.

- Manufacturing – Importing: Import and repackaging (EPA-calculated MOE = 31)
- Processing: Incorporation into adhesives and sealants (EPA-calculated MOE = 33)
- Processing: Incorporation into other formulations, mixtures, and reaction products (EPA-calculated MOE = 33)
- Industrial uses: Application of paints and coatings – non-spray application (EPA-calculated MOE = 33)
- Commercial uses: Use of laboratory chemicals – liquid (EPA-calculated MOE = 31)
- Commercial uses: Fabrication and Final Use of Products or Articles (EPA-calculated MOE = 45)
- Consumer Uses: Polyurethane Injection Resin (EPA-calculated MOE = 47)
- Consumer Uses: Specialty Wall Coverings (In-Place) (EPA-calculated MOE = 53)
- Consumer Uses: Indoor Furniture (EPA lowest calculated MOE = 31)
- Consumer Uses: Children's toys (legacy) (EPA-calculated MOE = 37)
- Consumer Uses: Children's toys (new) (EPA-calculated MOE = 90)
- Consumer Uses: Adult Toys (EPA-calculated MOE = 51).

In addition, the Draft Occupational Exposure Value Calculations in Appendix F for chronic exposure are similarly not scientifically defensible due to the failure to conduct BMD modeling in selecting a chronic POD.[74] At a minimum, the draft occupational exposure value must be recalculated after conducting BMD modeling for multiple candidate endpoints and selection of a POD based on the BMDL values.

d. EPA should apply best available methods to generate quantitative estimates of non-cancer risks for varying levels of exposure to DINP.

In its TSCA risk evaluations, EPA typically calculates a margin of exposure (MOE) for each condition of use (COU). The MOE is calculated as:

Margin of Exposure = Non-cancer point of departure / Human exposure.

The MOE approach is a scientifically deficient method for characterizing risk and is inconsistent with TSCA's requirements to use the "best available science"[75] and to ensure protection of "potentially exposed and susceptible subpopulations" ("PESS").[76]

Use of the MOE, which relies on a POD with no extrapolation to lower doses, is a simplistic approach that only compares the POD to the exposure level and judges whether this ratio is "interpreted as a human health risk of concern" or if "risk is not considered to be of concern and mitigation is not needed."[77] The MOE does not estimate the proportion of the exposed population projected to experience a specified health endpoint or the number of individuals

[74] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), p. 273.
[75] 15 U.S.C. §2625 (h).
[76] 15 U.S.C. §2602 (12).
[77] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), p. 139.

affected, and it perpetuates the scientifically flawed notion that a "safe" or "no risk" level of chemical exposure can be identified for a diverse exposed population.[78,79]

The National Academies[80] and the World Health Organization[81] ("WHO") have outlined more robust methods for risk estimation that more accurately account for variability and vulnerability across the human population and have been demonstrated in published case studies.[82,83,84,85] We applied the WHO methodology to the DINP liver toxicity endpoints of spongiosis hepatis (a type of liver lesion) and increased serum ALT (a biomarker indicating liver damage), using the BMD and BMDL values reported by EPA, to estimate risk-specific doses for several levels of incidence (e.g. 1%, 0.1%, etc.).

Our analysis (see Technical Appendix for details; all reported doses are HEDs) found that:

- 0.44 mg/kg-day is the lower bound (95% confidence) chronic human dose at which liver lesions are expected in 5% of the exposed population, and 0.17 mg/kg-day is the lower bound (95% confidence) chronic human dose at which reduced serum ALT is expected in 5% of the exposed population;
- 0.18 mg/kg-day is the lower bound (95% confidence) chronic human dose at which liver lesions are expected in 1% of the exposed population, and 0.065 mg/kg-day is the lower bound (95% confidence) chronic human dose at which reduced serum ALT is expected in 1% of the exposed population;
- 0.12 mg/kg-day is the lower bound (95% confidence) chronic human dose at which liver lesions are expected in 0.5% of the exposed population, and 0.04 mg/kg-day is the lower bound (95% confidence) chronic human dose at which reduced serum ALT is expected in 0.5% of the exposed population;
- 0.06 mg/kg-day is the lower bound (95% confidence) chronic human dose at which liver lesions are expected in 0.1% of the exposed population, and 0.02 mg/kg-day is the lower bound (95% confidence) chronic human dose at which reduced serum ALT is expected in 0.1% of the exposed population;

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[78] Woodruff, T. J., Rayasam, S. D. G., Axelrad, D. A., Koman, P. D., Chartres, N., et al.. (2023). A science-based agenda for health-protective chemical assessments and decisions: overview and consensus statement. Environ Health, 21(Suppl 1), 132. https://doi.org/10.1186/s12940-022-00930-3.

[79] McGartland, A., Revesz, R., Axelrad, D. A., Dockins, C., Sutton, P., Woodruff, T. J. (2017). Estimating the health benefits of environmental regulations. Science, 357(6350), 457-458. https://doi.org/10.1126/science.aam8204.

[80] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, Chapter 5.

[81] WHO. (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization project document 11, 2nd edition. https://www.who.int/publications/i/item/9789241513548.

[82] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. doi:10.1289/EHP3368.

[83] Nielsen, G. H., Heiger-Bernays, W. J., Levy, J. I., White, R. F., Axelrad, D. A., Lam, J., Chartres, N., Abrahamsson, D. P., Rayasam, S. D. G., Shaffer, R. M., Zeise, L., Woodruff, T. J., Ginsberg, G. L. (2023). Application of probabilistic methods to address variability and uncertainty in estimating risks for non-cancer health effects. Environ Health, 21(Suppl 1), 129. https://doi.org/10.1186/s12940-022-00918-z.

[84] Blessinger, T., Davis, A., Chiu, W. A., Stanek, J., Woodall, G. M., Gift, J., Thayer, K. A., Bussard, D. (2020). Application of a unified probabilistic framework to the dose-response assessment of acrolein. Environ Int, 143,105953. https://doi.org/10.1016/j.envint.2020.105953.

[85] Ginsberg, G. L. (2012). Cadmium risk assessment in relation to background risk of chronic kidney disease. J Toxicol Environ Health A, 75(7),374-390.

- 0.02 mg/kg-day is the lower bound (95% confidence) chronic human dose at which liver lesions are expected in 0.01% (1-in-10,000) of the exposed population, and 0.008 mg/kg-day is the lower bound (95% confidence) chronic human dose at which reduced serum ALT is expected in 0.01% of the exposed population;
- 0.01 mg/kg-day is the lower bound (95% confidence) chronic human dose at which liver lesions are expected in 0.001% (1-in-100,000) of the exposed population, and 0.003 mg/kg-day is the lower bound (95% confidence) chronic human dose at which reduced serum ALT is expected in 0.001% of the exposed population.

The implications of these risk values can be understood by comparison with the exposure levels considered by EPA to represent negligible risk. EPA's assessment uses a POD of 3.5 mg/kg-day (HED) and a benchmark MOE of 30,[86] meaning that EPA concludes "risk is not considered to be of concern and mitigation is not needed"[87] for any exposure below 0.12 mg/kg-day (3.5 mg/kg-day / 30 = 0.12 mg/kg-day). Our analysis finds that an exposure of 0.12 mg/kg-day is equal to the lower-bound dose for the 0.5% (1-in-200) risk level for spongiosis hepatis lesions, and an exposure of 0.12 mg/kg-day is greater than the lower-bound dose for the 1% (1-in-100) risk level increased serum ALT. These risks far exceed EPA's usual target range of protection for carcinogenic risks of 1-in-10,000 to 1-in-1,000,000.[88]

The risk values obtained from application of the WHO framework also indicate that many workers are at high risk for adverse non-cancer effects:

- High-end exposure estimates for 10 occupational exposure scenarios[89] are greater than 0.065 mg/kg/day, the lower-bound dose estimate for 1% (1-in-100) risk of reduced serum ALT, and are also greater than 0.06 mg/kg/day, the lower-bound dose estimate for 0.1% (1-in-1,000) risk of liver lesions: Manufacturing; Import/repackaging; Incorporation into adhesives and sealants; Incorporation into paints and coatings; Incorporation into other formulations, mixtures, and reaction products not covered elsewhere; PVC plastics compounding; Non-PVC material compounding; Application of adhesives and sealants; Application of paints and coatings; and Use of laboratory chemicals – liquid.
- The same 10 occupational exposure scenarios have central tendency exposure estimates[90] greater than 0.04 mg/kg/day, the lower-bound dose estimate for 0.5% (1-in-200) risk of reduced serum ALT.

The DINP Draft Risk Evaluation does not include tables of consumer exposure estimates, but Figures 4-9 to 4-12 indicate multiple COUs shave exposure estimates of approximately 0.1 mg/kg/day or greater, which exceed the lower-bound dose estimate for 1% (1-in-100) risk of reduced serum ALT, and are also greater than the lower-bound dose estimate for 0.1% (1-in-1,000) risk of liver lesions.

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[86] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), Table ES-1.
[87] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DIDP), p. 139.
[88] U.S EPA (2024). Unreasonable Risk Determination of the Draft Risk Evaluation for Formaldehyde, p. 13.
[89] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), Table 4-4.
[90] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), Table 4-4.

In addition, the risk values obtained from application of the WHO framework indicate the potential for high risks to the general population from fish consumption and soil contact. The DINP Draft Risk Evaluation estimate for DINP exposure for tribal populations using the "Heritage Ingestion Rate" is 0.037 mg/kg/day[91] and dermal exposure to DINP in soil is 0.045 mg/kg/day.[92] These exposure levels are greater than 0.02 mg/kg-day, the lower bound dose estimate for 0.1% (1-in-1,000) risk of reduced serum ALT.

EPA should apply the WHO framework to the DINP liver endpoints from the Lington *et al*. study. EPA should also conduct BMD modeling for other DINP candidate studies, and use the BMD outputs to apply the WHO framework to derive PODs and risk-specific doses for other non-cancer endpoints of DINP. The risk-specific dose estimates can in turn be used to characterize the risks associated with the estimated levels of DINP exposure.

4. EPA did not apply the best available science to identify and evaluate relevant and useful health effects studies for DINP.

a. EPA did not conduct a comprehensive and up-to-date literature search.

The need for transparent, consistent and comprehensive approaches to identifying health effects literature has been a key driver for increased adoption of systematic review methods in environmental health assessments over the past 15 years.[93,94,95] EPA's assessment of DINP is a concerning step backwards in this area, as the approach to identifying evidence is not clear, consistent or comprehensive. Based on the inconsistent procedures applied, it is unlikely that EPA would have identified and included all relevant health effects studies. This indicates critical deficiencies in the EPA systematic review protocol and the DINP Draft Hazard Assessment.

For the DINP Draft Hazard Assessment, EPA relied on non-EPA assessments of DINP completed in 2018 or earlier, and a literature search that was conducted in 2019 and has not been updated since. As stated in EPA's systematic review protocol for DINP:

> The search for peer-reviewed and gray literature relevant references was completed in September and May 2019, respectively.[96]

EPA has therefore not conducted a search for studies relevant to the DINP Draft Risk Evaluation in the five years prior to its release for public comment.

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[91] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), Table 4-12.
[92] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), Table 4-13.
[93] National Research Council (2011). Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.
[94] Woodruff TJ, Sutton P; Navigation Guide Work Group. An evidence-based medicine methodology to bridge the gap between clinical and environmental health sciences. Health Affairs 2011 May; 30(5):931-7.
[95] Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect 122:711–718.
[96] U.S. EPA (2024). Draft Systematic Review Protocol for Diisononyl Phthalate (DINP), p. 8.

For identifying epidemiological studies, EPA described its procedures as follows:

> To identify and integrate human epidemiologic data into the draft DINP Risk Evaluation, EPA first reviewed existing assessments of DINP conducted by regulatory and authoritative agencies… **most** of these assessments have been subjected to peer-review and/**or** public comment periods and have employed formal systematic review protocols.[97] (emphasis added)

> Next, EPA sought to identify new population, exposure, comparator, and outcome (PECO)-relevant literature published since the most recent existing assessment(s) of DINP by applying a literature inclusion cutoff date. For DINP, the applied cutoff date was based on existing assessments of epidemiologic studies of phthalates by Health Canada (2018a, b), which included literature up to January 2018….New PECO-relevant literature published between 2018 to 2019 was identified through the literature search conducted by EPA in 2019, as well as references published between 2018 to 2023 that were submitted with public comments to the DINP Docket…were evaluated for data quality.[98]

EPA therefore conducted a comprehensive literature search only for studies published in a time period of less than 2 years. As a result, the set of epidemiology studies consists of three inconsistent subsets:

- Studies published prior to January 2018 – are included in EPA's assessment only if they were included in the assessments conducted by other agencies. The assessments used by EPA to identify studies were not necessarily peer-reviewed and were not necessarily systematic reviews. EPA did not assess the quality of the studies identified by these other assessments. EPA did not consider any studies published before 2018 if they were not discovered by or not included in previous assessments for any reason.
- Studies published from January 2018 to September 2019 – EPA conducted its own search of the literature and applied its own inclusion/exclusion criteria.
- Studies published from September 2019 through 2023 – are included in EPA's assessment only if they were submitted to the EPA docket.

Thus, only those epidemiology studies published in a span of 21 months were identified and evaluated through a comprehensive process following an EPA protocol. For earlier studies (before 2018), EPA relied entirely on the Health Canada and other agency assessments and did not apply its own search, inclusion/exclusion and study evaluation procedures. For later studies (after September 2019), EPA did not conduct a search but included only those studies that were submitted by the public to EPA. This is not a clear, comprehensive or consistent approach to identifying the epidemiological evidence relevant to assessing the health effects of DINP. A

[97] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), p. 11.
[98] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), p. 12.

further concern is that these inconsistent procedures for identifying epidemiological evidence were ultimately relevant only to the identification of DINP hazards, since EPA subsequently excluded **all** epidemiological studies from consideration for dose-response assessment, without consideration of the merits of individual studies (see comment 3.a. above).

For identifying toxicology studies, EPA applied a similar process:

> EPA first reviewed existing assessments of DINP conducted by various regulatory and authoritative agencies…The purpose of this review was to identify sensitive and human relevant hazard outcomes associated with exposure to DINP, and identify key studies used to establish PODs for estimating human risk… **most** of these assessments have been subjected to external peer-review and/or public comment periods **but have not employed formal systematic review protocols**.[99] (emphasis added)

> EPA used the 2015 Health Canada assessment (EC/HC, 2015) as the key starting point for this draft document. The Health Canada assessment included scientific literature up to August 2014...Therefore, EPA considered literature published between 2014 to 2019 further…EPA reviewed new studies published between 2014 and 2019 and extracted key study information.[100]

EPA therefore conducted a comprehensive literature search only for studies published in a 5-year span. As a result, DINP toxicology studies are divided into three inconsistent subsets:

- Studies published up to mid-2014 – included only if they were included in the previous assessment by Health Canada. Additionally, EPA did not consider any studies published before mid-2014 if they were not discovered by or not included in the previous assessments for any reason.
- Relevant studies published from mid-2014 to September 2019 – EPA conducted its own search of the literature and applied its own inclusion/exclusion criteria.
- Studies published after September 2019 – were not considered at all.

Thus, only those toxicology studies published in a span of approximately 5 years were identified and evaluated through a comprehensive process following an EPA protocol (in this case, a protocol that is not yet available). For earlier toxicology studies (before mid-2014), EPA relied entirely on assessments by other agencies and did not apply its own search, inclusion/exclusion and study evaluation procedures. Toxicology studies published after September 2019 were not included at all. This is not a clear, comprehensive or consistent approach to identifying the toxicology evidence relevant to assessing the health effects of DINP.

For both epidemiology and toxicology, studies were treated differently based only on their date of publication. In addition, the procedures for epidemiology differed significantly from those for

[99] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), p. 16.
[100] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), p. 17.

toxicology; for example, some post-2019 epidemiology studies were included (but not necessarily all relevant studies, since a search was not conducted), whereas no post-2019 toxicology studies were included. Any toxicological findings on DINP published in the past 5 years were simply not considered by EPA, which is not consistent with the best available science; recent guidance on conducting systematic reviews in environmental health recommends that literature searches should be updated no more than 12 months before publication of a review.[101] Collectively, EPA's practices run a high risk of failing to include all relevant health effects studies and/or treating relevant studies differently in the DINP Draft Risk Evaluation.

b. EPA relied on assessments conducted by other agencies to exclude studies, without supporting justification.

EPA reviewed DINP health effects assessments conducted by Canada, Australia, multi-lateral European agencies, the U.S. Consumer Product Safety Commission (CPSC) and the U.S. National Toxicology Program (NTP) as part of conducting the DINP Draft Hazard Assessment. Epidemiology studies published before 2019 and toxicology studies published before mid-2014 were included in the TSCA risk evaluation only if they were included in these previous assessments. Studies that were not identified in searches conducted in the previous assessments and studies that were excluded from the previous assessments for any reason were not considered at all by EPA.

In principle, the use of previous assessments can be a useful part of conducting a TSCA risk evaluation, but the previous assessments must be carefully evaluated against a pre-specified set of criteria to determine whether they are of sufficient quality, and the resulting risk evaluation must still employ procedures that are transparent, comprehensive, consistent and unbiased, and must meet the TSCA section 26(h) scientific standards which direct that the Agency:

> Shall use scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science.[102]

However, EPA notes that the previous assessments it used were not systematic reviews, and not all were peer reviewed. EPA also does not provide adequate justification for its use of previous DINP assessments to substitute for conducting its own comprehensive systematic review to identify and evaluate health effects evidence.

The 2023 NASEM report *Building Confidence in New Evidence Streams for Human Health Risk Assessment* demonstrates an appropriate process for evaluating the quality of previous assessments. After conducting a comprehensive search for prior reviews satisfying a pre-specified PECO (population, exposure, comparator, outcome) statement, the NASEM applied AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) to assess the methodological

[101] P. Whaley, et al. Recommendations for the conduct of systematic reviews in toxicology and environmental health research (COSTER). Environment International 143 (2020), 105926. https://doi.org/10.1016/j.envint.2020.105926.
[102] 15 U.S.C. § 2625(h).

quality of each relevant review.[103] AMSTAR 2 was also applied by the NASEM in multiple prior reports on environmental health assessment.[104,105,106] In order to establish that it is appropriate to use previous assessments as part of a TSCA risk evaluation, EPA must apply this type of process to determine whether the previous assessments are consistent with the best available science, as required by TSCA.[107]

c. EPA used deficient inclusion and exclusion criteria for health effects evidence that inappropriately excluded important toxicity endpoints.

The DINP Draft Risk Evaluation does not provide the PECO statement that was used to identify epidemiology studies published from 2018-2019 and toxicology studies published from 2014-2019. The PECO statement is also not presented in the draft systematic review protocol for DINP. A PECO statement was provided in the broader 2021 TSCA Draft Systematic Review Protocol, which EPA has never revised to address public comments and more than 200 SACC recommendations.

PECO statements play a critical role in conducting a systematic review as they provide criteria for screening the literature search results to identify which studies are relevant (included in the risk evaluation) and not relevant (excluded from further consideration). The PECO statement for DINP is deficient and excludes a broad range of important toxicity outcomes from consideration in the draft risk evaluation.

The outcome component of the PECO statement for DINP health effects evidence provides the following criteria for inclusion and exclusion of studies:

> **Human:** All health outcomes (cancer and non-cancer) at the organ level or higher.
> **Animal and Plants:** All apical biological effects (effects measured at the organ level or higher)
> and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival, and growth.
> **Screener note:**
> - Measurable biological effects relevant for humans, animals and plants may include but are not limited to: mortality, behavioral, population, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects.
> - Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic.[108] (emphasis added)

[103] NASEM 2023). Building Confidence in New Evidence Streams for Human Health Risk Assessment: Lessons Learned from Laboratory Mammalian Toxicity Tests.
[104] NASEM (2019). Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene.
[105] NASEM (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations.
[106] NASEM (2022). Guidance on PFAS Exposure, Testing, and Clinical Follow-Up.
[107] 15 U.S.C. § 2625(h).
[108] U.S. EPA (2021). Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances, Table_Apx H-47.

By limiting the relevant human and animal studies to those with "apical" effects or those with effects at the "organ level or higher," EPA appears to be excluding studies of important biochemical markers and other outcomes at the cellular level that are strong indicators of hazards and which have commonly been used as critical effects in previous EPA hazard assessments, including TSCA risk evaluations (see examples below).

EPA's PECO statement provides very limited guidance for screeners on what effects are to be considered "apical" or "organ-level." The PECO says: "Apical endpoints include but are not limited to reproduction, survival, and growth" and "Measurable biological effects relevant for humans, animals and plants may include but are not limited to: mortality, behavioral, population, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects."[109] The 2021 TSCA Draft Systematic Review Protocol provides no further guidance on which outcomes are to be considered apical or organ-level, and which outcomes are to be considered cellular-level.

The NASEM has defined an apical end point as "An observable outcome in a whole organism, such as a clinical sign or pathologic state, that is indicative of a disease state that can result from exposure to a toxicant,"[110] and identified "tumors, birth defects, and neurologic impairments"[111] as examples. No biochemical measures or early biological changes were mentioned among the examples.

The definition of an apical effect appears to be narrower than the definition of an adverse effect provided by the EPA IRIS program: "a biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to response to an additional environmental challenge."[112] The definition of adverse effect includes, for example, "a biochemical change;" such effects appear to be excluded from the DINP Draft Risk Evaluation as they would likely be considered cellular-level effects rather than organ-level or apical effects.

Biochemical and/or cellular-level outcomes have been identified as critical effects in numerous past EPA hazard assessments, including some of the completed TSCA risk evaluations. Examples of these outcomes and past assessments include:

[109] U.S. EPA (2021). Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances, Table_Apx H-47.
[110] National Research Council (2007). Toxicity Testing in the 21st Century: A Vision and a Strategy, p. 38.
[111] National Research Council (2007). Toxicity Testing in the 21st Century: A Vision and a Strategy, p. 177.
[112] U.S. EPA. IRIS Glossary. https://www.epa.gov/iris/iris-glossary.

- reduced male fetal testosterone or adult male testosterone levels (2018 and 2019 IRIS staff published systematic reviews of health effects of phthalates, 2023 draft approach to cumulative risk assessment of phthalates under TSCA)[113,114,115]
- reduced thyroid hormone levels (2020 TSCA risk evaluation of HBCD; 2021 toxicity assessment of PFBS) [116,117]
- decreased erythrocyte counts and hemoglobin (2020 TSCA risk evaluation of perchloroethylene)[118]
- measures of immune function, such as increases in immunoglobulin E, lymphocytes, natural killer cells, and interlukin-4 levels (2020 TSCA risk evaluation of perchloroethylene)[119]
- decreased sperm quality or concentration (2020 TSCA risk evaluations of trichloroethylene and perchloroethylene; 2018 and 2019 IRIS staff published systematic reviews of health effects of phthalates)[120,121,122,123]
- acetylcholinesterase inhibition (numerous assessments of pesticides, including cumulative risk assessments of organophosphate and carbamate pesticides)[124,125]

EPA must either document that it has considered outcomes like altered thyroid hormone levels and other biochemical changes or cellular-level effects to be included in the animal and human evidence streams in the DINP Draft Risk Evaluation, or provide a justification for why these outcomes should not be considered as potential hazards of DINP.

Tagging biochemical and cellular-level outcomes as "supplemental, mechanistic," as directed in the PECO statement above, constrains the role of biochemical outcomes and other cellular changes to possibly providing biological support for apical outcomes, rather than considering precursors to apical outcomes as critical effects. Further, under EPA's proposed method, if no studies have been conducted of apical outcomes related to a biochemical outcome that has been

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[113] Radke EG, Braun JM, Meeker JD, Cooper GS. Phthalate exposure and male reproductive outcomes: A systematic review of the human epidemiological evidence. Environ Int. 2018 Dec;121(Pt 1):764-793.
[114] Yost EE, Euling SY, Weaver JA, Beverly BEJ, Keshava N, Mudipalli A, Arzuaga X, Blessinger T, Dishaw L, Hotchkiss A, Makris SL. Hazards of diisobutyl phthalate (DIBP) exposure: A systematic review of animal toxicology studies. Environ Int. 2019 Apr;125:579-594.
[115] U.S. EPA (2023). Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act, p. 102.
[116] U.S. EPA (2020). Risk evaluation for cyclic aliphatic bromide cluster (HBCD).
[117] U.S. EPA (2021). Human health toxicity values for perfluorobutane sulfonic acid and related compound potassium perfluorobutane sulfonate. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=350888.
[118] U.S. EPA (2020). Risk Evaluation for Percholorethylene (Ethene, 1,1,2,2-Tetrachloro-).
[119] U.S. EPA (2020). Risk Evaluation for Percholorethylene (Ethene, 1,1,2,2-Tetrachloro-).
[120] U.S. EPA (2020). Risk Evaluation for Trichloroethylene.
[121] U.S. EPA (2020). Risk Evaluation for Percholorethylene (Ethene, 1,1,2,2-Tetrachloro-).
[122] Radke EG, Braun JM, Meeker JD, Cooper GS. Phthalate exposure and male reproductive outcomes: A systematic review of the human epidemiological evidence. Environ Int. 2018 Dec;121(Pt 1):764-793.
[123] Yost EE, Euling SY, Weaver JA, Beverly BEJ, Keshava N, Mudipalli A, Arzuaga X, Blessinger T, Dishaw L, Hotchkiss A, Makris SL. Hazards of diisobutyl phthalate (DIBP) exposure: A systematic review of animal toxicology studies. Environ Int. 2019 Apr;125:579-594.
[124] U.S. EPA (2006). Organophosphorus cumulative risk assessment. https://www.regulations.gov/document/EPA-HQ-OPP-2006-0618-0002.
[125] U.S. EPA (2008). Revised N-methyl carbamate cumulative risk assessment. https://www.regulations.gov/document/EPA-HQ-OPP-2008-0347-0029.

studied, it is unclear whether the biochemical outcome will be considered at all. EPA says that supplemental studies "**may** be reviewed, evaluated for data quality, and incorporated into risk evaluations **as needed** for each chemical assessment"[126] (emphasis added), but it is unclear how a determination would be made to incorporate these studies into the risk evaluation, particularly in the absence of a related apical outcome study. Even if included to support a hazard conclusion based on apical outcomes, it appears that EPA rules out considering such studies for deriving a point of departure.

Exclusive reliance on studies of apical endpoints is also inconsistent with the best available science.[127] An important theme of the NASEM 2007 *Toxicity Testing in the 21st Century* report was that toxicity testing should move away from reliance on testing of apical outcomes. Accordingly, EPA's research programs and other U.S. health agencies have invested heavily in this new direction. Government and academic toxicology labs now rarely conduct studies of apical endpoints because the science has shifted towards examining more sensitive endpoints representing upstream biological changes ("key events") that lead to apical outcomes. In addition, a restriction to consider only apical or organ-level studies may bias the evidence base of the TSCA risk evaluations toward inclusion of industry-funded guidelines studies that are generally focused on apical endpoints.

d. EPA used multiple strategies to inappropriately exclude PECO-relevant health effects studies.

In past TSCA risk evaluations, EPA's practice was to exclude some health effects studies from consideration based on study quality evaluations; studies could be excluded based on a single perceived methodological shortcoming. EPA's draft systematic review protocol for DINP says that, in response to recommendations from the NASEM, SACC and public comments, all relevant studies are included:

> One main clarification is that *all references that undergo systematic review are considered for use in the risk evaluation*, even those that do not meet the various discipline and sub-discipline screening criteria or those that are categorized as supplemental information at title and abstract (TIAB) or full-text screening.[128]

This would be a welcome improvement to EPA's practice in TSCA risk evaluations; however, full consideration of EPA's systematic review procedures, as outlined in the draft protocol and hazard assessment, indicates that PECO-relevant health effects studies of DINP can be excluded from the risk evaluation, and relevant studies were excluded through multiple procedures—some of which lack scientific justification.

First, the systematic review protocol for DINP says EPA applied "further filtering" procedures to PECO-relevant health effects studies:

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[126] U.S. EPA (2021). Draft systematic review protocol supporting TSCA risk evaluations for chemical substances, p. 345.
[127] 15 U.S.C. § 2625(h).
[128] U.S. EPA (2024). Draft Systematic Review Protocol for Diisononyl Phthalate (DINP), p. 5.

> References that met the PECO screening criteria and were categorized as having epidemiology information and/or animal toxicity information for the evaluation of human health hazard went through a fit-for-purpose further filtering step to determine which studies would move forward to data quality evaluation and data extraction.[129]
>
> To streamline the identification of studies containing potentially relevant data that had not previously been evaluated by an authoritative agency, modifications were implemented to the process described in the 2021 Draft Systematic Review Protocol…Following PECO-based screening, references that met PECO screening criteria for epidemiology underwent a two-step further filtering process to identify the subset of potentially relevant references that proceeded to data quality evaluation.[130]
>
> The main purpose of this further filtering step was to allow for the refinement of the references that would be considered for data quality evaluation and extraction.[131]

The protocol does not provide any explanation for why the application of the PECO was insufficient for determining studies to include in the DINP Draft Risk Evaluation or why this "further filtering" process (which was not included in the 2021 TSCA draft systematic review method) was applied. It is also unclear why EPA found it necessary to "streamline" the process further when it was already extremely streamlined, with the most recent comprehensive literature search conducted in September 2019 and EPA's decision to expend very limited effort on pre-2018 epidemiology studies:

> Data quality evaluation and extraction wasn't conducted for any references published before 2018.[132]

Implementation of the further filtering step is also unclear. EPA provides a further filtering form for toxicology studies that includes a series of questions regarding the methods and outputs of a study. The form concludes with the Yes/No question "Should this reference move on to data extraction and evaluation?"[133] but no instructions are given for how the assessor is to answer this question.

EPA then says that 12 out of the 15 toxicology studies subjected to the further filtering procedure were excluded. Reasons provided for excluding these studies included:

> Some studies only included a single dose group…while others reported the sensitization effects of DINP on allergic/allergic dermatitis outcomes...The remaining studies were either mechanistic in scope…reproductive/development studies…or lack clarity in their results.[134]

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[129] U.S. EPA (2024). Draft Systematic Review Protocol for Diisononyl Phthalate (DINP), p. 21.
[130] U.S. EPA (2024). Draft Systematic Review Protocol for Diisononyl Phthalate (DINP), p. 21.
[131] U.S. EPA (2024). Draft Systematic Review Protocol for Diisononyl Phthalate (DINP), p. 24.
[132] U.S. EPA (2024). Draft Systematic Review Protocol for Diisononyl Phthalate (DINP), p. 21.
[133] U.S. EPA (2024). Draft Systematic Review Protocol for Diisononyl Phthalate (DINP), Tables 4-1.
[134] U.S. EPA (2024). Draft Systematic Review Protocol for Diisononyl Phthalate (DINP), p. 42.

It is not at all clear why these studies, already determined by EPA to be relevant to DINP, should be excluded from informing EPA's assessment of the hazards of DINP. It is particularly concerning that at least 3 reproductive/developmental toxicity studies – critical endpoints for phthalates and for assessment of risks to PESS – were excluded from the DINP Draft Risk Evaluation even though they were judged relevant. The "further filtering" considerations are implicit amendments to the PECO statement that were not made available for public comment or peer review before the assessment was conducted, which is contrary to best practices for systematic review and contradicts EPA's claim that all relevant studies are considered in the DINP Draft Risk Evaluation.

Second, studies that EPA deemed to be "uninformative" were not advanced to data extraction. The protocol states the EPA has continued its practice of excluding some studies based on study quality evaluations:

> Epidemiology references with an overall quality determination (OQD) of High, Medium, or Low underwent data extraction; data wasn't extracted from Uninformative references.[135]

EPA's choice not to conduct data extraction for some studies based on the overall quality determination is equivalent to excluding these studies from the risk evaluation, again contradicting EPA's claim that all relevant studies are considered in the risk evaluation. Further, EPA's labeling of relevant studies as "Uninformative" is inappropriate and lacking in justification.

EPA never explains, in either the draft systematic review protocol for DINP or the draft DINP hazard assessment, how an OQD is derived from the study quality metrics. A statement at the end of the data quality evaluation forms for both epidemiology and toxicology studies indicates that EPA uses an automatic calculation of the OQD:

> Specify which OQD you would give this paper (either confirm the **auto calculated judgement** OR suggest a new one based on your professional judgement?[136] (emphasis added)

However, there is no other mention of "auto calculated judgement" in the protocol or hazard assessment. Further, there is no guidance given on when and with what basis an OQD not based on auto-calculation may be assigned.

In addition, EPA's continued use of the term "Uninformative" as an overall study rating is highly problematic. EPA's recent draft TSCA risk evaluation for formaldehyde demonstrates that an EPA determination of "Uninformative" is extremely unreliable and should not be used as a basis to exclude studies.[137]

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[135] U.S. EPA (2024). Draft Systematic Review Protocol for Diisononyl Phthalate (DINP), p. 54.
[136] U.S. EPA (2024). Draft Systematic Review Protocol for Diisononyl Phthalate (DINP), Tables 5-5 and 5-7.
[137] U.S. EPA (2024). Draft Human Health Hazard Assessment for Formaldehyde.

For example, EPA's evaluation of study quality for oral toxicity studies of formaldehyde reveals the significant problems with assigning an OQD of "uninformative." EPA identified gastrointestinal effects as the most sensitive endpoint for oral exposure to formaldehyde. However, EPA classified the chronic oral exposure studies (by Til *et al*. and Tobe *et al*.) for gastrointestinal effects as "uninformative." After further consideration, EPA decided that these studies actually are informative, and that the Til *et al*. study should be used for dose-response analysis:

> Taken together, the three drinking water studies demonstrate a consistent pattern of gastrointestinal effects at comparable dose levels…While limitations in the two chronic drinking water studies resulted in OPPT data quality ratings of "uninformative for dose response" for the individual studies, the body of evidence across all three studies in combination increases the overall confidence in both the nature of the effects observed and the levels of formaldehyde exposure associated with those effects.[138]

> The three oral studies were selected to inform dose-response because they comprise the best available data on oral exposure to formaldehyde…when considered in conjunction with the other two studies, Til et al. 1989 contributes meaningful information to the WOE and dose-response despite the OPPT data quality rating of "uninformative."[139]

EPA's own analysis of its study quality ratings procedures therefore indicated that an overall study quality rating can be highly misleading and that labeling studies as "uninformative" or excluding studies based on the rating for a single study quality metric could erroneously lead to disregarding studies that constitute the best available science.

Accordingly, EPA must revise its approach to TSCA study quality evaluation to avoid disregarding studies based on pre-assigned labels that are unwarranted. By replacing the overall study quality determination with a domain- or metric-based approach, as the NASEM recommended for the TSCA program in 2021,[140] risk assessors can evaluate the ratings for each study in each domain at the evidence synthesis step to reach conclusions across the body of evidence, informed by the strengths and limitations of all relevant studies. These improved procedures should be applied to DINP and are necessary for consistency with EPA's claim that all relevant studies are considered in the risk evaluation.

Finally, EPA appears to have also excluded studies from the DINP Draft Risk Evaluation by other unexplained processes. Figure 4-6 of the draft systematic review protocol shows that out of 70 toxicology studies identified from previous hazard assessments of DINP, 60 were excluded from consideration and only 10 studies were included in the draft risk evaluation.[141] No explanation is provided for the exclusion of these studies.

These examples demonstrate that EPA has not implemented procedures consistent with its claim that "*all references that undergo systematic review are considered for use in the risk*

[138] U.S. EPA (2024). Draft Human Health Hazard Assessment for Formaldehyde, pp. 30-31.
[139] U.S. EPA (2024). Draft Human Health Hazard Assessment for Formaldehyde, p. 32.
[140] NASEM (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations, p. 36.
[141] U.S. EPA (2024). Draft Systematic Review Protocol for Diisononyl Phthalate (DINP), Figure 4-6, box 2a.

evaluation."[142] The TSCA systematic review process needs substantial revisions to correct a process that continues to exclude relevant evidence.

Further, many of the procedures described above for excluding studies were not disclosed prior to the SACC's review of the DINP Draft Hazard Assessment, since they are described only in the draft systematic review protocol that was not released until more than 4 weeks after the SACC meeting. The SACC was therefore unable to conduct a thorough review of the draft hazard assessment with full consideration of the underlying methods used to identify relevant health effects evidence.

e. EPA continues to use unclear terminology regarding evidence synthesis and integration.

EPA's use of unclear terminology for evidence synthesis and integration is an additional scientific shortcoming of the approach to systematic review for DINP. The NASEM has recommended the use of the term "evidence synthesis" for assembling the evidence and drawing conclusions from a single evidence stream (e.g. toxicology, epidemiology), and "evidence integration" for the subsequent process of drawing conclusions considering all evidence streams. The SACC review of EPA's 2021 Draft TSCA Method document reiterated this recommendation:

> The EPA did not follow the recommendation of NASEM to separate evidence synthesis from evidence integration. To quote NASEM: "Evidence synthesis deals with more homogeneous data within a single stream, and evidence integration deals with more heterogeneous data from multiple streams."[143]
>
> The EPA could improve the clarify, transparency, and efficiency of its process by adopting the NASEM recommendation to use "synthesis" for drawing conclusions separately for each evidence stream (i.e., human, animal, and mechanistic evidence) and use 'integration' for drawing conclusions considering all evidence streams in combination – in context of the risk evaluation process/needs.[144]

In the DINP systematic review protocol, however, EPA disregards the advice of both the NASEM and the SACC by continuing to use the term "evidence integration" for both steps.[145] The Draft DINP Hazard Assessment further confuses matters by using the term "hazard identification"[146] instead of "evidence integration."

This is one more area in which EPA's approach differs from best practices in systematic review, violating the best available science requirement under TSCA.[147] In addition, failing to adopt

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[142] U.S. EPA (2024). Draft Systematic Review Protocol for Diisononyl Phthalate (DINP), p. 5.
[143] U.S. EPA (2022). Science Advisory Committee on Chemicals Meeting Minutes and Final Report No. 2022-2, p. 83. https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0414-0044.
[144] U.S. EPA (2022). Science Advisory Committee on Chemicals Meeting Minutes and Final Report No. 2022-2, p. 88. https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0414-0044.
[145] U.S. EPA (2024). Draft Systematic Review Protocol for Diisononyl Phthalate (DINP), pp. 104-111.
[146] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), p. 23.
[147] 15 U.S.C. § 2625(h).

consistent and vetted terminology decreases the clarity of the risk evaluation and creates confusion for peer reviewers and the public regarding the procedures applied to drawing conclusions from a single stream of evidence.

f. EPA's approach to evidence integration lacks clear procedures and clearly-stated conclusions regarding the hazards of DINP.

EPA's TSCA risk evaluations lack a transparent and consistent approach to evidence integration. A key objective of the evidence integration process is to succinctly summarize the strength of the evidence concerning specific health endpoints and outcomes. This objective is advanced by pre-specifying a standard set of evidence descriptors. EPA's IRIS program handbook outlines a clear and consistent set of procedures for evidence synthesis and evidence integration that are applied in all IRIS assessments. The IRIS approach culminates in selection of a concise descriptor summarizing the strength of evidence for each hazard – selected from the standardized terms "evidence demonstrates," "evidence indicates," and "evidence suggests" as hazard conclusions.[148] No such terms are used in the DINP Draft Hazard Assessment. The TSCA risk evaluations do not demonstrate a consistent or structured process to evidence integration, and concise phrases to summarize the evidence are not standardized and vary significantly within and across risk evaluations. The hazard conclusions for DINP use concise but inconsistent and undefined phrases for some hazards, and longer ambiguous phrases for other hazards. Summary terms used by EPA for DINP hazards include:

- "consistent evidence"[149] (liver toxicity)
- "Some evidence"[150] (neurotoxicity)
- "limited evidence"[151] (cardiovascular health effects and musculoskeletal toxicity)
- "DINP has consistently been shown to cause developmental effects in animal models"[152]
- "DINP lacks estrogenic potential *in vivo*"[153]
- For kidney toxicity, no phrasing representing an overall conclusion is provided; the clearest attempt at summarizing the evidence says, "Findings were similar across study designs… EPA is considering kidney toxicity for dose-response analysis."[154]
- For immune system toxicity, no phrasing representing an overall conclusion is provided; the clearest attempt at summarizing the evidence says, "Although available studies of laboratory animals provide evidence for immune adjuvant effects of DINP in sensitized animals, EPA is not further considering these effects for dose-response assessment or for use in extrapolating human risk."[155]

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[148] U.S. EPA (2022). ORD Staff Handbook for Developing IRIS Assessments, Table 6-7.
[149] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), p. 43.
[150] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), p. 58.
[151] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), p. 61 and p. 68.
[152] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), p. 42.
[153] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), p. 42.
[154] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), pp. 50-51.
[155] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), p. 67.

Without further standardization and definition of terms, it is difficult for readers to gain a clear, concise understanding of EPA's hazard conclusions. It is unclear, for example, if "consistent evidence" is equivalent to "strong evidence," or whether "findings were similar across study designs" is equivalent to "consistent evidence."

EPA should adopt a standardized procedure, such as the approach used by the IRIS program, for evidence integration for all DINP endpoints, including a pre-specified set of descriptors that are considered for each endpoint.

g. EPA released an incomplete draft systematic review protocol for DINP that was not made publicly available in advance of the draft risk evaluation.

Along with the DINP Draft Risk Evaluation, EPA released a chemical-specific systematic review protocol as a supplemental file. Publication of a chemical-specific protocol is consistent with best available scientific methods in systematic review and responds to recommendation of the NASEM and the SACC. However, the comments above demonstrate many flaws and deficiencies in the protocol and the procedures applied to conducting the risk evaluation. Public release of the protocol for public comment and peer review in advance of conducting the risk evaluation would have provided an opportunity for early identification and correction of the many critical deficiencies described above. For future TSCA risk evaluations, EPA must publish a chemical-specific systematic review protocol for public comment before completing the draft risk evaluation, as recommended by the Institute of Medicine and the NASEM as a best practice for systematic review.[156,157]

The TSCA program should follow the established procedures of EPA's IRIS program, which makes a draft protocol for each assessment publicly available in advance of its release for public comment. Following the public comment process, the IRIS program then publishes an updated protocol, as needed. For example, for the IRIS assessments of five per- and polyfluoroalkyl substances ("PFAS"), a draft protocol was made available for public comment for 45 days. The IRIS program then followed up with a revised protocol to address public comments, with documentation of the changes, that was published before the release of the PFAS draft assessments.[158] EPA should be following this same approach for all TSCA risk evaluations.

h. EPA should prepare a new TSCA systematic review handbook that is aligned with the best available scientific methods and issue updated draft systematic review protocols for all risk evaluations currently in development.

To adhere to best practices in systematic review, including those recommended by the NASEM and SACC, EPA should issue a new TSCA systematic review methodology document that states methods to be applied consistently to all TSCA risk evaluations. EPA should also prepare a chemical-specific systematic review protocol for each TSCA risk evaluation it conducts, and these protocols should be complete, stand-alone documents that do not refer to the 2021 Draft

[156] Institute of Medicine (2011). Finding what works in health care: Standards for systematic reviews.
[157] National Research Council (2014). Review of EPA's Integrated Risk Information System (IRIS) process.
[158] U.S. EPA (2021). Systematic Review Protocol for the PFAS IRIS Assessments. https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=345065 (accessed 1 February 2024).

TSCA Method for critical elements. The chemical-specific protocols for ongoing and future risk evaluations should also be released for public comment well before the draft risk evaluations are completed to allow for public input, scrutiny, and opportunities for improvement. We urge EPA to consistently adopt the practices of the IRIS program for systematic review protocol development and publication across all EPA programs and offices.

5. EPA failed to adequately identify potentially exposed or susceptible subpopulations (PESS), as required by TSCA.

EPA has failed to meet its requirement under TSCA to identify, consider, and account for risk to "potentially exposed or susceptible subpopulations" ("PESS") in the DINP Draft Risk Evaluation.[159] EPA excluded multiple potential PESS, and among the PESS identified, EPA did not apply a transparent methodology for quantifying the risk of harm to each identified PESS using the best available science. This omission is consistent with previous risk evaluations where EPA regularly underestimated the risk to PESS due to a lack of adequate identification and consideration of PESS. By not adequately identifying and considering risks to PESS, EPA is violating TSCA's requirements. EPA must therefore adopt a consistent framework for identifying PESS and quantifying the risk of harm to PESS from DINP exposures.

Identification and consideration of PESS for each chemical assessed is a critical aspect of conducting risk evaluation under TSCA, as TSCA requires EPA to:

> determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs or other nonrisk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation.[160]

In the final 2024 TSCA Risk Evaluation Framework Rule, EPA defined PESS as:

> Potentially exposed or susceptible subpopulation means a group of individuals within the general population identified by EPA who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, the elderly, or overburdened communities.[161]

EPA needs to develop and apply a consistent approach to identify all PESS. To date, EPA has not employed a consistent or structured approach to identifying PESS in its TSCA risk evaluations, including scope documents for ongoing risk evaluations. EPA's approach and terminology for identifying PESS varied considerably in the first 10 TSCA risk evaluations. These inconsistencies included differences in whether health conditions related to a chemical's hazards were considered in identifying PESS; and whether fenceline communities were included as

[159] 15 U.S.C. §2605(b)(4)(A).
[160] 15 U.S.C. §2605(b)(4)(A).
[161] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act, § 702.33.

PESS.[162] To remedy the problem of inconsistent and incomplete identification of PESS, Rayasam *et al.* recommended that:

> EPA should prepare a comprehensive methodology to identify PESS and quantify their risks consistently within and across the TSCA risk evaluations.[163]

EPA has not yet proposed such a methodology. The DINP Draft Risk Evaluation is particularly deficient in its failure to present any structured approach for identification of PESS. The DINP Draft Risk Evaluation indicates that the following groups were identified as PESS:

> women of reproductive age, pregnant women, infants, children and adolescents, people who frequently use consumer products and/or articles containing high concentrations of DINP, people exposed to DINP in the workplace, and tribes whose diets include large amounts of fish.[164]

The recent DIDP Draft Risk Evaluation, while also deficient in identifying PESS, does include consideration of various categories of "biological susceptibility" in Table 7-1 of the draft hazard assessment document, which is a useful initial step towards developing a consistent, structured approach to identifying PESS in TSCA risk evaluations.[165] The DINP Draft Risk Evaluation provides no similar table or any other demonstration that EPA has thoroughly considered the various factors that may increase susceptibility to DINP. EPA has thus taken a step backwards with the exclusion of more detailed evaluations of PESS based on both greater exposure and greater susceptibility that were included in recent risk evaluations. DIDP Table 7-1 gave explicit consideration to each of the following: lifestage, pre-existing disease or disorder, lifestyle activities, socio-demographic factors, nutrition, genetics/epigenetics, and other chemical and non-chemical stressors. However, EPA failed to fully consider all PESS within each category identified for DIDP,[166] and did even less for DINP.

The DINP Draft Risk Evaluation and its various supporting documents do not indicate that any consideration was given to many of the susceptibility factors that were considered in the discussion of PESS identification for DIDP, including pre-existing disease or disorder, lifestyle activities, socio-demographic factors, nutrition, genetics/epigenetics, and other chemical and non-chemical stressors.

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[162] Rayasam, S. D. G., Koman, P. D., Axelrad, D. A., Woodruff, T. J., Chartres, N. (2022). Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States. Environmental science & technology, 56(17), 11969–11982. https://doi.org/10.1021/acs.est.2c02079.

[163] Rayasam, S. D. G., Koman, P. D., Axelrad, D. A., Woodruff, T. J., Chartres, N. (2022). Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States. Environmental science & technology, 56(17), 11969–11982. https://doi.org/10.1021/acs.est.2c02079].

[164] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), p. 12.

[165] U.S. EPA (2024). Draft Human Health Hazard Assessment for Diisodecyl Phthalate (DIDP), p. 61, Table 7-1.

[166] U.S. EPA (2024). Draft Human Health Hazard Assessment for Diisodecyl Phthalate (DIDP), p. 61, Table 7-1.

Further, the DINP Draft Risk Evaluation does not provide any careful consideration of how its risk estimates should be adjusted to account for risks to susceptible groups. The full discussion of this issue is:

> EPA used a value of 10 for the UF_H to account for human variability. The Risk Assessment Forum, in *A Review of the Reference Dose and Reference Concentration Processes*, discusses some of the evidence for choosing the default factor of 10 when data are lacking—including toxicokinetic and toxicodynamic factors as well as greater susceptibility of children and elderly populations.[167]

This statement is also a step backward from the acknowledgement in other recent risk evaluations that a 10-fold factor is likely insufficient to account for the extent of human variability in response to hazardous chemical exposures. For example, the final TCEP risk evaluation includes language similar to the quote above, but goes on to elaborate on the uncertainties of the default value, including susceptibility factors not accounted for:

> EPA used a default value of 10 for human variability (UF_H) to account for increased susceptibility when quantifying risks from exposure to TCEP. The Risk Assessment Forum, in *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002b), discusses some of the evidence for choosing the default factor of 10 when data are lacking and describe the types of populations that may be more susceptible, including different lifestages (*e.g.,* of children and elderly). U.S. EPA (2002b), however, did not discuss all the factors presented in [the TCEP risk evaluation]. Thus, **uncertainty remains regarding whether these additional susceptibility factors would be covered by the default UF_H value of 10** chosen for use in the TCEP risk evaluation. In addition, given that EPA is using a default UF_H in the absence of data regarding whether adverse effects from TCEP exposure differ for certain subpopulations (such as those with genetic polymorphisms or underlying diseases), **it is also not known whether the chosen default UF_H would fully cover pre-existing diseases or disorders**.[168] (emphasis added)

In fact, the WHO and other authoritative bodies have demonstrated that the traditional 10X uncertainty factor is insufficient for fully accounting for risk in sensitive groups and recommend the use larger uncertainty factors.[169,170] Instead of increasing the use of uncertainty factors to account for the wide range of vulnerability and variability in the human population, EPA uses

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[167] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), p. 175.
[168] U.S. EPA (2024). Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), pp. 462-463.
[169] WHO. (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization project document 11, 2nd edition. https://www.who.int/publications/i/item/9789241513548.
[170] Varshavsky, J. R., Rayasam, S. D. G., Sass, J. B., Axelrad, D. A., Cranor, C. F., Hattis, D., Hauser, R., Koman, P. D., Marquez, E. C., Morello-Frosch, R., Oksas, C., Patton, S., Robinson, J. F., Sathyanarayana, S., Shepard, P. M., & Woodruff, T. J. (2023). Current practice and recommendations for advancing how human variability and susceptibility are considered in chemical risk assessment. Environmental Health, 21(Suppl 1), 133. https://doi.org/10.1186/s12940-022-00940-1.

inadequate default uncertainty factors, which will result in an underestimation of risk, particularly for PESS.

For the identified PESS, EPA also concluded that, due to a lack of chemical specific data for each PESS, no further adjustment is necessary. TSCA does not require chemical-specific quantitative data to identify or evaluate risks to PESS. Instead, TSCA requires EPA to rely on the "best available science" when evaluating risks to PESS. The best available science demonstrates that both intrinsic factors, which include biological traits like age, genetic makeup, and pre-existing health conditions, and extrinsic factors, which include psychosocial stress from experiencing income inequality, violence, racism, healthcare inequity, or food insecurity, can individually or collectively increase susceptibility to harm from chemical exposures.[171]

EPA should therefore focus first on identifying susceptible subpopulations based on either chemical-specific evidence or the broader literature on intrinsic and extrinsic susceptibility factors, and then, as a separate step, consider how to adequately account for the elevated risks for each group, in some cases by using scientifically-supported uncertainty factors. The initial identification of PESS, however, should not be contingent on chemical-specific data. Once the appropriate groups are identified as PESS, EPA should then consider the availability of chemical-specific data. When such data are absent, the application of appropriate adjustment factors (beyond the customary 10x factor for human variability) should be applied to ensure that risks to PESS are not underestimated.[172]

6. EPA's approach systematically underestimates DINP exposure and risk.

a. EPA failed to conduct a background exposure assessment, underestimating risk to potentially exposed or susceptible subpopulations.

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[171] Woodruff, T. J., Rayasam, S. D. G., Axelrad, D. A., Koman, P. D., Chartres, N., Bennett, D. H., Birnbaum, L. S., Brown, P., Carignan, C. C., Cooper, C., Cranor, C. F., Diamond, M. L., Franjevic, S., Gartner, E. C., Hattis, D., Hauser, R., Heiger-Bernays, W., Joglekar, R., Lam, J., … Zeise, L. (2023). A science-based agenda for health-protective chemical assessments and decisions: Overview and consensus statement. Environmental Health,21(1), 132. https://doi.org/10.1186/s12940-022-00930-3; Rachel Morello-Frosch et al., Understanding the Cumulative Impacts of Inequalities in Environmental Health: Implications for Policy, 30 Health Affs. 879 (2011), https://www.healthaffairs.org/doi/pdf/10.1377/hlthaff.2011.0153; Cliona M. McHale et al., Assessing Health Risks from Multiple Environmental Stressors: Moving from G×E to I×E, 775 Mutational Rsch. 11 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5863617/; Devon C. Payne-Sturges et al., Methods for Evaluating the Combined Effects of Chemical and Nonchemical Exposures for Cumulative Environmental Health Risk Assessment, 15 Int'l. J. Env't Rsch. & Pub. Health 2797 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6313653/; Gilbert C. Gee et al., Environmental Health Disparities: A Framework Integrating Psychosocial and Environmental Concepts, 112 Env't Health Persps. 1645 (2004), https://doi.org/10.1289/ehp.7074; Gina M. Solomon et al., Cumulative Environmental Impacts: Science and Policy to Protect Communities 37 Ann. Rev. Pub. Health 83, 87–88 (2016), https://www.annualreviews.org/doi/pdf/10.1146/annurev-publhealth-032315-021807; Patricia D. Koman et al., Population Susceptibility: A Vital Consideration in Chemical Risk Evaluation Under the Lautenberg Toxic Substances Control Act, 17 PLoS Biology 1, 4 (2019), https://journals.plos.org/plosbiology/article?id=10.1371/.

[172] Varshavsky et al. Current Practice and Recommendations for Advancing How Human Variability and Susceptibility Are Considered in Chemical Risk Assessment, 21(Suppl 1) Env't Health Article No. 133, at 3 (2023), https://doi.org/10.1186/s12940-022-00940-1.

Phthalates such as DINP have become ubiquitous contaminants worldwide to which the general population is commonly exposed through multiple pathways, including water, air, and inhalation and/or ingestion of household dust.[173] DINP is primarily used as a plasticizer to make flexible polyvinyl chloride (PVC). It is also used to make building and construction materials, automotive care and fuel products, and other commercial and consumer products such as adhesives, sealants, paints, coatings, and electrical products.[174]

However, EPA failed to account for these multiple sources of exposure in the DINP Draft Risk Evaluation. Instead, EPA stated that certain significant pathways of exposure to the general population, including food and food packaging materials, were not be considered because they constitute "non-TSCA" uses.[175] EPA's rationale for this decision is that these other pathways of exposure will be assessed and managed by statutes such as the Clean Air Act and the Federal Food, Drug, and Cosmetic Act. However, exposures via these pathways are highly relevant and reasonably foreseeable across the human population, and cannot be excluded when evaluating the human health risks posed by DINP. EPA is required under TSCA to account for all "reasonably foreseeable" pathways of exposure.[176] EPA must also conduct risk evaluations using "scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science."[177] The NASEM recommends consideration of background exposures when conducting a risk evaluation for both individual chemicals and categories of chemicals through a cumulative risk assessment,[178] citing that background exposures at "even small doses may have a relevant biological effect."[179]

Given the widespread exposure to DINP across the general population and susceptible populations through food, plastic food storage products, nail polishes, and other "non-TSCA" uses, the failure to consider exposures from those uses would be contrary to TSCA's requirements to consider all reasonably foreseeable exposure pathways and to identify and address risks to PESS. While EPA may not be able to directly regulate some uses under TSCA, EPA cannot adequately evaluate the conditions of use that are subject to TSCA regulation or control their unreasonable risks if it ignores the background exposures that potentially contribute to a baseline level of DINP in the human body. EPA's reliance on existing statutes outside of TSCA to manage exposure pathways for the general population and potentially exposed or susceptible subpopulations will result in underestimated risk and is scientifically unsupported.

The SACC criticized the omission of background exposures from the recent DINP Draft Risk Evaluation:

> Total exposure to phthalates is much more complex and involves many exposure sources, including those beyond the regulatory authority of Toxic Substances Control Act (TSCA). However, those exposures should be included as "background" or some other

[173] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), p. 10.
[174] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), p. 10.
[175] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), p. 11.
[176] 15 U.S.C. §2602 (4).
[177] 15 U.S.C. § 2625(h).
[178] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, pp. 135, 136, and 214.
[179] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 130.

> designation, rather than being invisible in the risk assessment. The science should not be redacted because of legislative compartmentalization of the contributors to real risk.[180]

In the preamble to the 2024 final risk evaluation framework rule, EPA acknowledged the importance of background exposures, and that these exposures can be incorporated in TSCA risk evaluations:

> it may be appropriate to consider potential background exposures from non-TSCA uses that are not within the scope of the risk evaluation as part of an aggregate exposure assessment. Likewise, EPA could consider the disproportionate impacts that background exposures may have on overburdened communities to inform the final unreasonable risk determination.[181]

EPA routinely considers exposures from products or sources that it does not regulate in assessments. For example, in its assessment and regulation of the pesticide fumigant sulfuryl fluoride, EPA's Office of Pesticide Programs ("OPP") considered all sources of exposure to fluoride, including ones EPA does not regulate (such as toothpaste). Considering these exposures was critical for accurate risk calculation and decision making—OPP proposed to terminate pesticidal uses of sulfuryl fluoride because children's total exposure to fluoride (mainly from drinking water and toothpaste) exceeded the risk cup of acceptable exposure levels.[182] EPA's plan to exclude from consideration uses of DINP subject to statutes such as the Federal Food Drug and Cosmetics Act ignores the reality of human exposure and violates TSCA.

Thus, EPA must revise the DINP Draft Risk Evaluation so it addresses all sources and pathways of DINP exposure, including background exposures. TSCA, with its specific charge to consider potentially exposed or susceptible subpopulations, has a critical role to play in the protection of the general public and more susceptible groups such as infants and toddlers that are facing DINP exposure. As we have previously detailed, established scientific principles for exposure assessment require that all known pathways of exposures be included in the assessment, or exposure will not be accurately quantified, and risk will be underestimated, particularly to potentially exposed or susceptible subpopulations.[183]

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[180] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," p. 16.

[181] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act.

[182] Sulfuryl Fluoride; Proposed Order Granting Objections to Tolerances and Denying Request for Stay, 76 Fed. Reg. 3,422-01 (Jan. 19, 2011).

[183] US EPA. (2019). Draft Toxic Substances Control Act (TSCA) Risk Evaluations and TSCA Science Advisory Committee on Chemicals (SACC); Cyclic Aliphatic Bromide Cluster (HBCD) and 1,4 Dioxane; Notice of Availability and Public Meetings. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0059 and https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0056.

b. EPA considered aggregate exposure to only a limited extent.

The DINP Draft Risk Evaluation states:

> EPA defines aggregate exposure as "the combined exposures to an individual from a chemical substance across multiple routes and across multiple pathways (40 CFR § 702.33)." For the draft DINP risk evaluation, EPA considered aggregate risk across all routes of exposure for each individual consumer and occupational COU evaluated for acute, intermediate, and chronic exposure durations. EPA did not consider aggregate exposure for the general population. As described in Section 4.1.3, EPA employed a risk screen approach for the general population exposure assessment. Based on results from the risk screen, no pathways of concern (*i.e.,* ambient air, surface water, drinking water, fish ingestion) to DINP exposure were identified for the generation population.
>
> EPA did not consider aggregate exposure scenarios across COUs because the Agency did not find any evidence to support such an aggregate analysis, such as statistics of populations using certain products represented across COUs, or workers performing tasks across COUs. However, EPA considered combined exposure across all routes of exposure for each individual occupational and consumer COU to calculate aggregate risks.[184]

In an important improvement, EPA considered aggregate exposure to DINP by combining worker exposure estimates for the inhalation and dermal routes of exposure, and consumer exposure estimates for the inhalation, ingestion and dermal routes of exposure. Due to this minimal implementation of aggregate exposure assessment, EPA was able to identify certain COUs as posing high risk that would not have satisfied EPA's decision criteria without aggregation.

EPA's approach, however, does not fully characterize aggregate exposure and the resulting risks. EPA considered exposures to only individual COUs without combining exposures to multiple COUs or exposures that occur to the same individuals in different settings. EPA aggregated across DINP exposure pathways for consumers and separately for workers, but it did not aggregate exposures for workers who also experience consumer and general population exposures, and did not aggregate exposures for consumers who have exposure to multiple consumer products or who experience general population exposures. EPA says that these exposures were not aggregated because it did not have data indicating such co-exposures.

EPA should not require chemical-specific evidence to conduct aggregate exposure assessment. It can reasonably model scenarios in which exposures are combined across products and across worker, consumer and general population exposures. For example, some individuals with occupational exposure to DINP are likely to live close to where they work and would therefore also be exposed as members of the general population, and may also use DINP-containing consumer products.

[184] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), p. 134.

By failing to recognize that some individuals may be exposed in multiple ways – that is, experiencing combinations of general population, consumer and worker exposures – EPA is systematically underestimating exposures and risks to some of the most-exposed people in the population. This approach is not consistent with the requirements of TSCA to apply the best available science,[185] and to identify and eliminate unreasonable risks to potentially exposed or susceptible subpopulations,[186] which include groups with higher exposure levels. TSCA also requires EPA to eliminate unreasonable risks resulting from "the manufacture, processing, distribution in commerce, use, or disposal of a chemical substance…or…any combination of such activities."[187] EPA can meet these TSCA requirements only by fully considering aggregate exposures. If EPA does not estimate risks from aggregate exposures across COUs and exposure settings in the final DINP risk evaluation, the resulting underestimation would then be a consideration that must be incorporated into the unreasonable risk determination.

[185] 15 USC §2625(h).
[186] 15 U.S.C. §2605(b)(4)(A).
[187] 15 U.S.C. §2605(a).

Technical Appendix: Application of IPCS framework to DINP non-cancer risks

In the *Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP)*, EPA selected liver toxicity as the most sensitive endpoint for estimation of risks from chronic oral exposures.

For risk characterization of non-cancer health effects, TSCA risk evaluations calculate a "margin of exposure" (MOE) for each exposure scenario, which is the ratio of the point of departure (POD) to the exposure level. For the DINP liver effects, the DINP draft hazard assessment concludes that a benchmark MOE of 30[188] indicates that "risk is not considered to be of concern and mitigation is not needed."[189] EPA's approach to risk characterization does not actually estimate risks of adverse effects in the population, but instead simply applies a "bright line" judgment of whether or not the MOE is adequate. A more informative approach for both risk characterization and risk management would be to apply the probabilistic dose-response assessment methods of the International Programme on Chemical Safety (IPCS),[190] part of the World Health Organization (WHO), to estimate the risk of adverse effects at various levels of exposure. The IPCS methodology has previously been described and applied in several peer-reviewed journal articles.[191,192,193,194,195]

We applied the IPCS approach for "quantal-deterministic" and continuous endpoints and the "approximate probabilistic" calculation (see IPCS report Fig 3.5, panel C)[196] to estimate risks of two DINP liver toxicity endpoints: spongiosis hepatis (a type of liver lesion) and increased serum ALT (a biomarker indicating liver damage).

The analysis involved the following steps:

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[188] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), Table ES-1.

[189] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), p. 139.

[190] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition.

[191] Chiu WA, Slob W. A Unified Probabilistic Framework for Dose–Response Assessment of Human Health Effects. Environmental Health Perspectives, 2015 December;123(12): 1241–1254. doi:10.1289/ehp.1409385

[192] Nielsen, G. H., Heiger-Bernays, W. J., Levy, J. I., White, R. F., Axelrad, D. A., Lam, J., Chartres, N., Abrahamsson, D. P., Rayasam, S. D. G., Shaffer, R. M., Zeise, L., Woodruff, T. J., Ginsberg, G. L. (2023). Application of probabilistic methods to address variability and uncertainty in estimating risks for non-cancer health effects. Environ Health, 21(Suppl 1), 129. https://doi.org/10.1186/s12940-022-00918-z

[193] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. doi:10.1289/EHP3368

[194] Blessinger T, Davis A, Chiu WA, Stanek J, Woodall GM, Gift J, Thayer KA, Bussard D. Application of a unified probabilistic framework to the dose-response assessment of acrolein. Environment International, 2020 October;143:105953. doi: 10.1016/j.envint.2020.105953

[195] Chiu WA, Paoli GM. Recent Advances in Probabilistic Dose–Response Assessment to Inform Risk-Based Decision Making. Risk Analysis, 2021 April;41(4):596-609. doi: 10.1111/risa.13595

[196] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition.

1. Derivation of IPCS POD and corresponding uncertainty adjustments
2. Application of interspecies adjustments
3. Application of intraspecies adjustments
4. Calculation of HD_M^I - the human dose (HD) of DINP associated with a particular magnitude of effect M at a particular population incidence I.

For each aspect of the analysis, including the values used to derive the IPCS POD and the adjustment factors applied to derive the HD_M^I, the IPCS methodology uses a 50th percentile value (P50) as a central estimate and the ratio of 95th percentile to 50th percentile (P95/P50) as a measure of uncertainty. All POD and HD_M^I values presented in this analysis are for continuous exposures.

We demonstrate each of these steps starting with the EPA-estimated benchmark dose (BMD) values in applied dose units to derive a set of oral HD_M^I values for different levels of population incidence (e.g. 1%, 0.1%, etc.). Although EPA has selected a NOAEL for liver toxicity as the chronic POD for DINP rather than the statistically-estimated BMD, EPA guidance states that BMDs are preferable to NOAELs for characterizing dose-response relationships (see main comments above).

STEP 1: Derivation of IPCS POD and corresponding uncertainty adjustments

EPA conducted BMD modeling for several liver endpoints from a study by Lington et al. The two most sensitive endpoints were spongiosis hepatis and increased serum ALT at 6 month sacrifice. BMD results were as follows:

EPA benchmark dose modeling results for two liver toxicity endpoints from LIngton et al. 1977

Endpoint	Benchmark Response (BMR)	BMD	BMDL
Spongiosis hepatis[a]	10% relative deviation	31.88 mg/kg-d	8.57 mg/kg-d
Increased serum ALT at 6-month sacrifice[b]	1 standard deviation change from controls	23.42 mg/kg-d	15.50 mg/kg-d

[a] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), Table_Apx E-15.
[b] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), Table_Apx E-7.

In the IPCS methodology, the BMD is the central estimate (P50), and uncertainty in the BMD (P95/P50) is equal to the ratio of BMD / BMDL:

BMD/BMDL (spongiosis hepatis) = 31.88 / 8.57 = 3.72
BMD/BMDL (increased serum ALT) = 23.42 / 15.50 = 1.51.

In the IPCS methodology, spongiosis hepatis is classified as a quantal-deterministic endpoint. The IPCS methodology requires the use of an ED_{50} (median effective dose) value as the POD for quantal-deterministic endpoints. Since an ED_{50} is not available from the EPA risk evaluation, we began with the BMD, and applied adjustments provided by the IPCS methodology: "if ED50 not reported: BMD at the reported BMR is multiplied by an additional factor of 3.0; additional uncertainty through adding 1.5^2 to $(P95/P50)^2$."[197] For increased serum ALT, a continuous endpoint, no adjustment to the ED_{50} is applied and the BMD is used as the POD in applying the IPCS framework.

The values applied for determining the IPCS POD and its uncertainty for each endpoint are entered in the IPCS approximate probabilistic calculation template as follows:

Determination of point of departure (POD) and its uncertainty[a] for probabilistic dose-response analysis of chronic oral exposure to DINP: liver toxicity				
Aspect	**Spongiosis hepatis**		**Increased serum ALT**	
	P50	**P95/P50**	**P50**	**P95/P50**
BMD	31.9 mg/kg-d	3.72	23.4 mg/kg-d	1.51
BMD-to-ED_{50} adjustment	3	1.5	N/A[b]	N/A[b]
IPCS POD = ED_{50}	**95.6 mg/kg-d**	**3.95[c]**	**23.4 mg/kg-d**	**1.51**

[a] Uncertainty is expressed as the ratio of the 95th percentile (P95) to the 50th percentile (P50)
[b] Not applicable
[c] (Composite P95/P50) = $10^{[(\log 3.72)^2 + (\log 1.5)^2]^{0.5}} = 3.95$

[197] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. Figure 4. doi:10.1289/EHP3368

Step 2: Application of interspecies (animal-to-human) adjustments

For interspecies (animal-to-human) adjustments, the IPCS methodology first considers a factor for body-size scaling, and then a factor for remaining toxicokinetic (TK) and toxicodynamic (TD) differences. The IPCS framework provides equations for calculating the body size scaling adjustment factor, based on the assumed human body weight and test species body weight. We applied EPA's assumptions for human body weight (80 kg) and rat body weight (0.25 kg)[198] to derive the appropriate central tendency (P50) factor and its uncertainty (P95/P50).

For the TK/TD differences remaining after bodyweight scaling, the IPCS report recommends a central estimate (P50) of 1 (i.e., no additional interspecies differences) and representing uncertainty with a P95/P50 factor of 3.[199] We incorporated these IPCS recommendations, which are entered In the IPCS approximate probabilistic calculation template as follows:

Interspecies adjustments for probabilistic dose-response analysis of chronic oral exposure to DINP: liver toxicity		
Aspect	**P50**	**P95/P50**
$AF_{Interspecies\text{-}BS}$	5.64[a]	1.26[a]
$AF_{Interspecies\text{-}TK/TD}$	1	3
[a] Calculated from IPCS equation 4-2 using EPA assumptions regarding body weight of humans (80 kg) and rats (0.25 kg).		

Step 3: Application of intraspecies (human variability) adjustments

In the IPCS methodology, the value of the human variability adjustment factor ($AF_{intraspecies}$) varies depending on the incidence of the adverse effect in the exposed population – with a larger adjustment factor necessary to extrapolate from the POD to lower levels of incidence. The IPCS report provides $AF_{intraspecies}$ for several incidence (I) values. The P50 and P95/P50 values for $AF_{intraspecies}$ provided by IPCS for several values of I, along with additional values of I of interest for this analysis, are provided in the following table:

[198] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), Appendix F.
[199] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.3.

Lognormal approximation of uncertainty distributions for intraspecies variability ($AF_{Intraspecies}$) for varying levels of population incidence (I)		
Incidence (I)	**$AF_{Intraspecies}$**	
	P50	**P95/P50**
10%[a]	3.49	2.24
5%[a]	4.98	2.82
1%[a]	9.69	4.32
0.5% (1-in-200)[a]	12.36	5.06
0.1% (1-in-1,000)[a]	20.42	6.99
0.01% (1-in-10,000)[a]	37.71	10.39
0.001% (1-in-100,000)[b]	64.25	14.65

[a] IPCS Table 4.5
[b] Calculated for this analysis using the same methods that were used to derive IPCS Table 4.5

Step 4: Calculation of HD_M^I

The output of the IPCS methodology is generically described as an HD_M^I value – the human dose (HD) associated with a particular magnitude of effect M at a particular population incidence I. For this analysis, the "M" represents either spongiosis hepatis or increased serum ALT. The following tables present the HD_M^I results for I = 10%, 5%, 1%, 0.1%, 0.01%, and 0.001% using the POD, $AF_{Interspecies}$, and $AF_{Intraspecies}$ values shown above.

The IPCS approach is a probabilistic method, so the HD_M^I is a distribution; selected values from that distribution are presented in the tables as follows:

- P05: 5th percentile estimate (lower confidence limit) of HD_M^I (this value is shown in **bold**)
- P50: 50th percentile estimate (median) of HD_M^I
- P95: 95th percentile estimate (upper confidence limit) of HD_M^I.

All HD_M^I values in the following tables are human equivalent doses (HEDs), as they incorporate interspecies body size scaling (see Step 2 above).

Calculation of HD_M^I from chronic DINP exposure: liver toxicity (Incidence = 10%)				
Aspect	**Spongiosis hepatis**		**Increased serum ALT**	
	P50	**P95/P50**	**P50**	**P95/P50**
BMD	31.9 mg/kg-d	3.72	23.4 mg/kg-d	1.51
BMD-to-ED_{50} adjustment	3	1.5	N/A	N/A
IPCS POD = ED_{50}	**95.6 mg/kg-d**	**3.95[c]**	**23.4 mg/kg-d**	**1.51**
$AF_{Interspecies-BS}$	5.64	1.26	5.64	1.26
$AF_{Interspecies-TK/TD}$	1	3	1	3
$AF_{Intra-I=10\%}$	3.49	2.24	3.49	2.24
HD_M^I	4.9 mg/kg-d[a]	7.0[b]	1.2 mg/kg-d[a]	4.2[c]
	P05	**P95**	**P05**	**P95**
$HD_M^{I\,(d)}$	**0.7 mg/kg-d**	34 mg/kg-d	**0.3 mg/kg-d**	5 mg/kg-d

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 3.95)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 2.24)^2]^{0.5}} = 7.0$
[c] (Composite P95/P50) = $10^{[(\log 1.51)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 2.24)^2]^{0.5}} = 4.2$
[d] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50). HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic DINP exposure: liver toxicity (Incidence = 5%)				
Aspect	**Spongiosis hepatis**		**Increased serum ALT**	
	P50	**P95/P50**	**P50**	**P95/P50**
BMD	31.9 mg/kg-d	3.72	23.4 mg/kg-d	1.51
BMD-to-ED_{50} adjustment	3	1.5	N/A	N/A
IPCS POD = ED_{50}	**95.6 mg/kg-d**	**3.95[c]**	**23.4 mg/kg-d**	**1.51**
$AF_{Interspecies-BS}$	5.64	1.26	5.64	1.26
$AF_{Interspecies-TK/TD}$	1	3	1	3
$AF_{Intra-I=5\%}$	4.98	2.82	4.98	2.82
HD_M^I	3.4 mg/kg-d[a]	7.8[b]	0.8 mg/kg-d[a]	4.9[c]
	P05	**P95**	**P05**	**P95**
$HD_M^{I\,(d)}$	**0.44 mg/kg-d**	27 mg/kg-d	**0.17 mg/kg-d**	4 mg/kg-d

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 3.95)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 2.82)^2]^{0.5}} = 7.8$
[c] (Composite P95/P50) = $10^{[(\log 1.51)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 2.82)^2]^{0.5}} = 4.9$
[d] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50). HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic DINP exposure: liver toxicity (Incidence = 1%)				
Aspect	**Spongiosis hepatis**		**Increased serum ALT**	
	P50	**P95/P50**	**P50**	**P95/P50**
BMD	31.9 mg/kg-d	3.72	23.4 mg/kg-d	1.51
BMD-to-ED_{50} adjustment	3	1.5	N/A	N/A
IPCS POD = ED_{50}	**95.6 mg/kg-d**	**3.95[c]**	**23.4 mg/kg-d**	**1.51**
$AF_{Interspecies-BS}$	5.64	1.26	5.64	1.26
$AF_{Interspecies-TK/TD}$	1	3	1	3
$AF_{Intra-I=1\%}$	9.69	4.32	9.69	4.32
HD_M^I	1.7 mg/kg-d[a]	10.0[b]	0.04 mg/kg-d[a]	6.6[c]
	P05	**P95**	**P05**	**P95**
$HD_M^{I\,(d)}$	**0.18 mg/kg-d**	17 mg/kg-d	**0.06 mg/kg-d**	2.8 mg/kg-d

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 3.95)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 4.32)^2]^{0.5}} = 10.0$
[c] (Composite P95/P50) = $10^{[(\log 1.51)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 4.32)^2]^{0.5}} = 6.6$
[d] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50). HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic DINP exposure: liver toxicity (Incidence = 0.5%)				
Aspect	**Spongiosis hepatis**		**Increased serum ALT**	
	P50	**P95/P50**	**P50**	**P95/P50**
BMD	31.9 mg/kg-d	3.72	23.4 mg/kg-d	1.51
BMD-to-ED_{50} adjustment	3	1.5	N/A	N/A
IPCS POD = ED_{50}	**95.6 mg/kg-d**	**3.95[c]**	**23.4 mg/kg-d**	**1.51**
$AF_{Interspecies-BS}$	5.64	1.26	5.64	1.26
$AF_{Interspecies-TK/TD}$	1	3	1	3
$AF_{Intra-I=0.5\%}$	12.36	5.06	12.36	5.06
HD_M^I	1.4 mg/kg-d[a]	11.0[b]	0.34 mg/kg-d[a]	7.5[c]
	P05	**P95**	**P05**	**P95**
$HD_M^{I\,(d)}$	**0.12 mg/kg-d**	15 mg/kg-d	**0.04 mg/kg-d**	2.5 mg/kg-d

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 3.95)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 5.06)^2]^{0.5}} = 11.0$
[c] (Composite P95/P50) = $10^{[(\log 1.51)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 5.06)^2]^{0.5}} = 7.5$
[d] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50). HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic DINP exposure: liver toxicity (Incidence = 0.1%)				
Aspect	**Spongiosis hepatis**		**Increased serum ALT**	
	P50	**P95/P50**	**P50**	**P95/P50**
BMD	31.9 mg/kg-d	3.72	23.4 mg/kg-d	1.51
BMD-to-ED_{50} adjustment	3	1.5	N/A	N/A
IPCS POD = ED_{50}	**95.6 mg/kg-d**	**3.95[c]**	**23.4 mg/kg-d**	**1.51**
$AF_{Interspecies-BS}$	5.64	1.26	5.64	1.26
$AF_{Interspecies-TK/TD}$	1	3	1	3
$AF_{Intra-I=0.1\%}$	20.42	6.99	20.42	6.99
HD_M^I	0.8 mg/kg-d[a]	13.9[b]	0.2 mg/kg-d[a]	9.8[c]
	P05	**P95**	**P05**	**P95**
$HD_M^{I\,(d)}$	**0.06 mg/kg-d**	12 mg/kg-d	**0.02 mg/kg-d**	2.0 mg/kg-d

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 3.95)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 6.99)^2]^{0.5}} = 13.9$
[c] (Composite P95/P50) = $10^{[(\log 1.51)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 6.99)^2]^{0.5}} = 9.8$
[d] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50). HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic DINP exposure: liver toxicity (Incidence = 0.01%)				
Aspect	**Spongiosis hepatis**		**Increased serum ALT**	
	P50	**P95/P50**	**P50**	**P95/P50**
BMD	31.9 mg/kg-d	3.72	23.4 mg/kg-d	1.51
BMD-to-ED_{50} adjustment	3	1.5	N/A	N/A
IPCS POD = ED_{50}	**95.6 mg/kg-d**	**3.95[c]**	**23.4 mg/kg-d**	**1.51**
$AF_{Interspecies-BS}$	5.64	1.26	5.64	1.26
$AF_{Interspecies-TK/TD}$	1	3	1	3
$AF_{Intra-I=0.01\%}$	37.71	10.39	37.71	10.39
HD_M^I	0.4 mg/kg-d[a]	18.9[b]	0.1 mg/kg-d[a]	13.9[c]
	P05	**P95**	**P05**	**P95**
$HD_M^{I\,(d)}$	**0.02 mg/kg-d**	8 mg/kg-d	**0.008 mg/kg-d**	1.5 mg/kg-d

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 3.95)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 10.39)^2]^{0.5}} = 18.9$
[c] (Composite P95/P50) = $10^{[(\log 1.51)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 10.39)^2]^{0.5}} = 13.9$
[d] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50). HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic DINP exposure: liver toxicity (Incidence = 0.001%)				
Aspect	**Spongiosis hepatis**		**Increased serum ALT**	
	P50	**P95/P50**	**P50**	**P95/P50**
BMD	31.9 mg/kg-d	3.72	23.4 mg/kg-d	1.51
BMD-to-ED_{50} adjustment	3	1.5	N/A	N/A
IPCS POD = ED_{50}	**95.6 mg/kg-d**	**3.95[c]**	**23.4 mg/kg-d**	**1.51**
$AF_{Interspecies-BS}$	5.64	1.26	5.64	1.26
$AF_{Interspecies-TK/TD}$	1	3	1	3
$AF_{Intra-I=0.001\%}$	64.25	14.65	64.25	14.65
HD_M^I	0.3 mg/kg-d[a]	25.0[b]	0.06 mg/kg-d[a]	18.9[c]
	P05	**P95**	**P05**	**P95**
$HD_M^{I\,(d)}$	**0.01 mg/kg-d**	7 mg/kg-d	**0.003 mg/kg-d**	1.2 mg/kg-d

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 3.95)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 14.65)^2]^{0.5}} = 25.0$
[c] (Composite P95/P50) = $10^{[(\log 1.51)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 14.65)^2]^{0.5}} = 18.9$
[d] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50). HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Interpretation of Results

The National Academies and the WHO/IPCS have both recommended using the lower confidence limit (LCL) on a probabilistic dose-response distribution for use in decision-making, in place of a traditional reference dose (RfD) or reference concentration (RfC). The National Academies said in *Science and Decisions* that:

> Multiple risk-specific doses could be provided…in the various risk characterizations that EPA produces to aid environmental decision-making.[200]
>
> A Risk-Specific Reference Dose: For quantal effects, the RfD can be defined to be the dose that corresponds to a particular risk specified to be de minimis (for example, 1 in 100,000) at a defined confidence level (for example, 95%) for the toxicity end point of concern.[201]

The WHO/IPCS said:

[200] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 140.
[201] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 140.

> The LCL of the HD_M^I can be used as a probabilistic RfD to replace the deterministic RfD. In this case, the probabilistic RfD is the dose that protects the population from a specified magnitude and incidence of effect with a pre-specified per cent coverage (confidence).[202]

Consistent with the guidance from the National Academies and the IPCS, we summarize the above results by focusing on the lower confidence limit (5th percentile or P05) risk-specific doses (HD_M^I) for multiple levels of risk (incidence or I).

Based on application of the WHO/IPCS methodology to DINP liver effects from chronic exposures, we find that:

- 0.44 mg/kg-day is the lower bound (95% confidence) chronic human dose at which liver lesions are expected in 5% of the exposed population, and 0.17 mg/kg-day is the lower bound (95% confidence) chronic human dose at which reduced serum ALT is expected in 5% of the exposed population
- 0.18 mg/kg-day is the lower bound (95% confidence) chronic human dose at which liver lesions are expected in 1% of the exposed population, and 0.065 mg/kg-day is the lower bound (95% confidence) chronic human dose at which reduced serum ALT is expected in 1% of the exposed population
- 0.12 mg/kg-day is the lower bound (95% confidence) chronic human dose at which liver lesions are expected in 0.5% of the exposed population, and 0.04 mg/kg-day is the lower bound (95% confidence) chronic human dose at which reduced serum ALT is expected in 0.5% of the exposed population
- 0.06 mg/kg-day is the lower bound (95% confidence) chronic human dose at which liver lesions are expected in 0.1% of the exposed population, and 0.02 mg/kg-day is the lower bound (95% confidence) chronic human dose at which reduced serum ALT is expected in 0.1% of the exposed population
- 0.02 mg/kg-day is the lower bound (95% confidence) chronic human dose at which liver lesions are expected in 0.01% (1-in-10,000) of the exposed population, and 0.008 mg/kg-day is the lower bound (95% confidence) chronic human dose at which reduced serum ALT is expected in 0.01% of the exposed population
- 0.01 mg/kg-day is the lower bound (95% confidence) chronic human dose at which liver lesions are expected in 0.001% (1-in-100,000) of the exposed population, and 0.003 mg/kg-day is the lower bound (95% confidence) chronic human dose at which reduced serum ALT is expected in 0.001% of the exposed population.

[202] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, p. 12.

The implications of these risk values can be understood by comparison with the exposure levels considered by EPA to represent negligible risk. EPA's assessment uses a POD of 3.5 mg/kg-day (HED) and a benchmark MOE of 30,[203] meaning that EPA concludes "risk is not considered to be of concern and mitigation is not needed"[204] for any DINP exposure below 0.12 mg/kg-day (3.5 mg/kg-day / 30 = 0.12 mg/kg-day). Our analysis indicates that an exposure of 0.12 mg/kg-day is equal to the lower-bound dose for the 0.5% (1-in-200) risk level for spongiosis hepatis lesions, and an exposure of 0.12 mg/kg-day is greater than the lower-bound dose for the 1% (1-in-100) risk level increased serum ALT. These risks far exceed EPA's usual target range of protection for carcinogenic risks of 1-in-10,000 to 1-in-1,000,000.[205]

The estimates of HD_M^I presented here were based entirely on input values and equations available from the WHO/IPCS methodology document and related publications, and from EPA's *Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP)*. An important caveat to these calculations is that the values used to represent human variability may be understated. The IPCS default human variability distribution is based on 37 data sets for human toxicokinetic variability and 34 data sets for human toxicodynamic variability. Most of these data sets were obtained from controlled human exposure studies of pharmaceuticals conducted in small samples of healthy adults, representing considerably less variability than found in the general population.[206,207,208] If human variability is underestimated, then the actual dose associated with each incidence level (e.g. I =1%, I = 0.1%) will be lower than the values obtained from this analysis – or in other words, risk at each dose will be underestimated.

[203] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP), Table ES-1.
[204] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), p. 139.
[205] U.S. EPA (2024). Unreasonable Risk Determination of the Draft Risk Evaluation for Formaldehyde, p. 13.
[206] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition.
[207] Hattis, D., Lynch, M.K. (2007). Empirically observed distributions of pharmacokinetic and pharmacodynamic variability in humans—Implications for the derivation of single-point component uncertainty factors providing equivalent protection as existing reference doses. In Lipscomb, J.C. & Ohanian, E.V. (Eds.), *Toxicokinetics in risk assessment* (pp. 69-93). Taylor & Francis Group. https://doi.org/10.1201/b14275.
[208] Axelrad, D. A., Setzer, R. W., Bateson, T. F., DeVito, M., Dzubow, R. C., Fitzpatrick, J. W., Frame, A. M., Hogan, K. A., Houck, K., Stewart, M. (2019). Methods for evaluating variability in human health dose-response characterization. Hum Ecol Risk Assess, 25, 1-24. https://doi.org/10.1080/10807039.2019.1615828.